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(54) Naphthyloxyacetic acid derivatives as PGE2 agonists and antagonists

Naphthylessigsäurederivate als PGEZ Agonisten und Antagonisten

Dérivés de l'acide naphtylacétique comme agonistes et antagonistes de PGEZ

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(56) References cited:
EP-A- 0 253 257
EP-A- 0 270 929

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Description

This invention relates to naphthyloxyacetic acid derivatives, processes for their preparation and pharmaceutical compositions containing them.

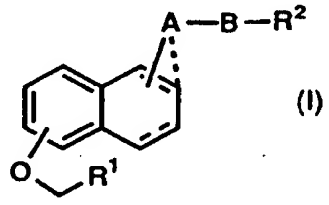
As prostaglandin (PG)E_2 agonists, many compounds have been known including PGE_2 per se or its derivatives. However, no compounds which antagonize PGE_2 or inhibit PGE_2 activity have been known until now.

PGE_2 has been known as a metabolite in the arachidonate cascade. Its known activities include uterine contractile activity, a pain-inducing effect, a promoting effect on digestive peristalsis, an awaking effect, a suppressive effect on gastric acid secretion, and hypotensive activity. Antagonist or agonist activites on these effects would be expected to confer the following activities on a compound.

To antagonize PGE_2 means to suppress the effects above mentioned, so PGE_2 antagonists are considered to inhibit uterine contraction, to have analgetic action, to inhibit digestive peristalsis, or to induce sleep. Therefore, PGE_2 antagonists are considered to be useful as analgesics, antidiarrheals, sleep inducers or for the prevention of abortion.

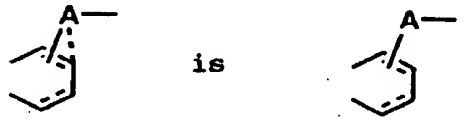
To agonize for PGE_2 means to promote the effects above mentioned, so PGE_2 agonists are considered to stimulate uterine contraction, to promote digestive peristalsis, to suppress gastric acid secretion, or to lower blood pressure. Therefore, PGE_2 agonists are considered to be useful as abortifacients, cathartics, and antiulcer, anti-gastritis or antihypertensive agents.

The present invention accordingly provides naphthyloxyacetic acid derivatives of the formula (I):

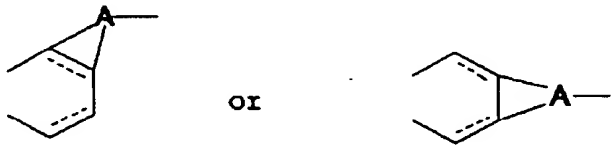


(I)

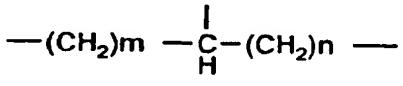
wherein R^1 is (i) $-COOR^4$ in which R^4 is hydrogen or C1-4 alkyl, (ii) $-CONR^5R^6$ in which R^5 and R^6 each, independently, is hydrogen, C1-4 alkyl or C1-4 alkyl substituted by a hydroxy group or (iii) $-CH_2OH$;



in which A is a bond or C1-4 alkylene, or

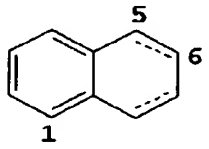


in which A is



in which m is 0, 1, 2, 3 or 4, n is 0, 1, 2, 3 or 4, and m + n is 2, 3 or 4;

B is $-NR^3SO_2-$ or $-SO_2NR^3-$ in which R^3 is hydrogen, C1-4 alkyl or $-CH_2COOR^7$ in which R^7 is hydrogen or a group R^{4a} in which R^{4a} is C1-4 alkyl;
R^2 is (i) C1-6 alkyl, C2-6 alkenyl or C2-6 alkynyl, or
(ii) C1-6 alkyl, C2-6 alkenyl or C2-6 alkynyl substituted by one, two, or three substituents selected from phenyl, C4-7 cycloalkyl or phenyl substituted by one, two or three substituents selected from C1-4 alkyl, C1-4 alkoxy or halogen and
in the formula



⎯ is a single bond or double bond;

or a non-toxic salt thereof.

In the formula (I), C1-4 alkyl represented by R^3, R^4, R^{4a}, R^5, R^6, means methyl, ethyl, propyl, butyl and isomeric groups thereof.

In the formula (I), C1-6 alkyl represented by R^2 means methyl, ethyl, propyl, butyl, pentyl, hexyl and isomeric groups thereof.

In the formula (I), C2-6 alkenyl represented by R^2 means vinyl, propenyl, butenyl, pentenyl, hexenyl and isomeric groups thereof.

In the formula (I), C2-6 alkynyl represented by R^2 means ethynyl, propynyl, butynyl, pentynyl, hexynyl and isomeric groups thereof.

In the formula (I), C4-7 cycloalkyl represented in R^2 means cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl.

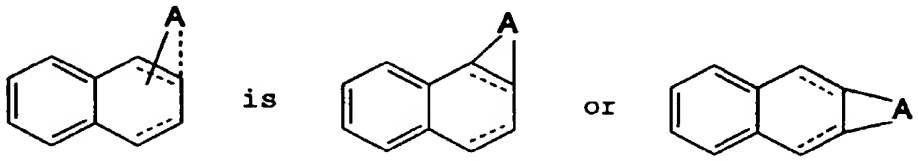
In the formula (I), C1-4 alkyl represented as substituents of phenyl in R^2 means methyl, ethyl, propyl, butyl and isomeric groups thereof.

In the formula (I), C1-4 alkoxy represented as substituents of phenyl in R^2 means methoxy, ethoxy, propoxy, butoxy and isomeric groups thereof.

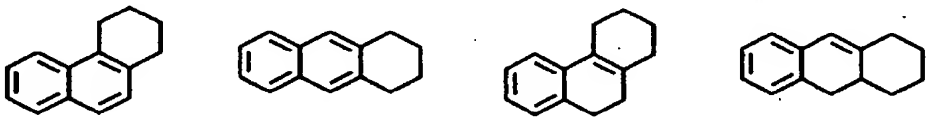
In the formula (I), halogen represented as substituents of phenyl in R^2 means fluorine, chlorine, bromine and iodine.

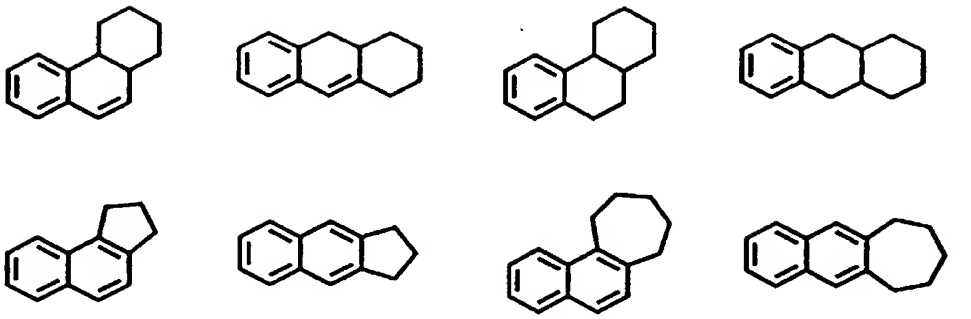
In the formula (I), C1-4 alkylene represented by A means methylene, ethylene, trimethylene or tetramethylene and isomeric groups thereof.

In the formula (I), the ring represented by



for example



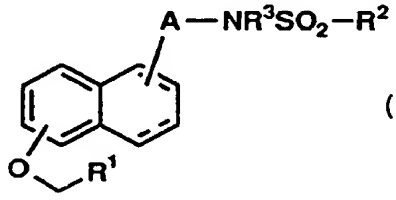


Unless otherwise, specified all isomers are included in the invention. For example, alkyl, alkylene and alkenylene includes straight-chain or branched-chain ones. Double bond in alkenylene include E, Z and E, Z mixtures. Isomers generated by asymmetric carbon(s) e.g. branched alkyl are in the present invention.

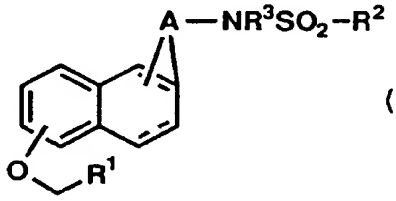
In formula (I) the group

is preferably attached to the 1-position. The group A is preferably attached to the 5-, 6- or 5- and 6-positions.

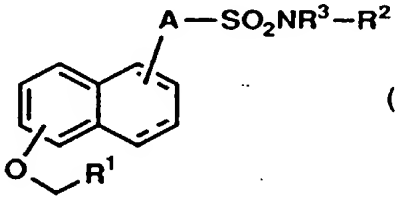
In the compounds of the present invention of the formula (I), the compounds described in the Examples and the following compounds are preferred.



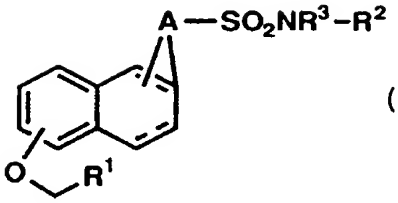
(Ia)



(Ib)



(Id)

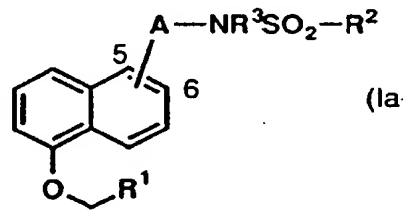


(Ie)

wherein all the symbols are as hereinbefore defined.

Especially preferred compounds are the compounds described in the Examples and the following compounds.

(Ia-1)



(Ia-1)

R^1	A	R^3	R^2
-COOH	5-bond	hydrogen	2,2-diphenylethyl
-COOH	5-bond	hydrogen	2-naphthyl
-COOH	5-bond	hydrogen	2-(4-methoxyphenyl)vinyl
-COOH	5-bond	hydrogen	2-(4-chlorophenyl)vinyl
-COOH	5-bond	hydrogen	2-phenyl-2-(4-methoxyphenyl)vinyl
-COOH	5-bond	hydrogen	2-phenyl-2-(4-chlorophenyl)vinyl
-COOH	5-bond	hydrogen	2-(4-methoxyphenyl)ethyl
-COOH	5-bond	hydrogen	2-(4-chlorophenyl)ethyl
-COOH	5-bond	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	5-bond	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl
-COOH	5-bond	methyl	2-phenylvinyl
-COOH	5-bond	methyl	2,2-diphenylvinyl
-COOH	5-bond	methyl	2-phenylethyl
-COOH	5-bond	methyl	2,2-diphenylethyl
-COOH	5-bond	methyl	pentyl
-COOH	5-bond	methyl	2-naphthyl
-COOH	5-bond	methyl	2-(4-methoxyphenyl)vinyl
-COOH	5-bond	methyl	2-(4-chlorophenyl)vinyl
-COOH	5-bond	methyl	2-phenyl-2-(4-methoxyphenyl)vinyl
-COOH	5-bond	methyl	2-phenyl-2-(4-chlorophenyl)vinyl
-COOH	5-bond	methyl	2-(4-methoxyphenyl)ethyl

(continued)

R^1	A	R^3	R^2
-COOH	5-bond	methyl	2-(4-chlorophenyl)ethyl
-COOH	5-bond	methyl	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	5-bond	methyl	2-phenyl-2-(4-chlorophenyl)ethyl
-COOH	5-bond	$-CH_2COOH$	2-phenylvinyl
-COOH	5-bond	-CH2COOH	2,2-diphenylvinyl
-COOH	5-bond	-CH2COOH	2-phenylethyl
-COOH	5-bond	$-CH_2COOH$	2,2-diphenylethyl
-COOH	5-bond	$-CH_2COOH$	pentyl
-COOH	5-bond	$-CH_2COOH$	2-naphthyl
-COOH	5-bond	$-CH_2COOH$	2-(4-methoxyphenyl)vinyl
-COOH	5-bond	$-CH_2COOH$	2-(4-chlorophenyl)vinyl
-COOH	5-bond	$-CH_2COOH$	2-phenyl-2-(4-methoxyphenyl)vinyl
-COOH	5-bond	$-CH_2COOH$	2-phenyl-2-(4-chlorophenyl)vinyl
-COOH	5-bond	$-CH_2COOH$	2-(4-methoxyphenyl)ethyl
-COOH	5-bond	$-CH_2COOH$	2-(4-chlorophenyl)ethyl
-COOH	5-bond	$-CH_2COOH$	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	5-bond	$-CH_2COOH$	2-phenyl-2-(4-chlorophenyl)ethyl
-COOH	$5-CH_2CH_2$	hydrogen	pentyl
-COOH	$5-CH_2CH_2$	hydrogen	2-naphthyl
-COOH	$5-CH_2CH_2$	hydrogen	2-(4-methoxyphenyl)vinyl
-COOH	$5-CH_2CH_2$	hydrogen	2-(4-chlorophenyl)vinyl
-COOH	$5-CH_2CH_2$	hydrogen	2-phenyl-2-(4-methoxyphenyl)vinyl
-COOH	$5-CH_2CH_2$	hydrogen	2-phenyl-2-(4-chlorophenyl)vinyl
-COOH	$5-CH_2CH_2$	hydrogen	2-(4-methoxyphenyl)ethyl
-COOH	$5-CH_2CH_2$	hydrogen	2-(4-chlorophenyl)ethyl
-COOH	$5-CH_2CH_2$	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	$5-CH_2CH_2$	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl
-COOH	$5-CH_2CH_2$	methyl	2,2-diphenylvinyl
-COOH	$5-CH_2CH_2$	methyl	2-phenylethyl
-COOH	$5-CH_2CH_2$	methyl	2,2-diphenylethyl
-COOH	$5-CH_2CH_2$	methyl	pentyl
-COOH	$5-CH_2CH_2$	methyl	2-naphthyl
-COOH	$5-CH_2CH_2$	methyl	2-(4-methoxyphenyl)vinyl
-COOH	$5-CH_2CH_2$	methyl	2-(4-chlorophenyl)vinyl
-COOH	$5-CH_2CH_2$	methyl	2-phenyl-2-(4-methoxyphenyl)vinyl
-COOH	$5-CH_2CH_2$	methyl	2-phenyl-2-(4-chlorophenyl)vinyl
-COOH	$5-CH_2CH_2$	methyl	2-(4-methoxyphenyl)ethyl
-COOH	$5-CH_2CH_2$	methyl	2-(4-chlorophenyl)ethyl

(continued)

R^1	A	R^3	R^2
-COOH	5-CH_2CH_2	methyl	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	5-CH_2CH_2	methyl	2-phenyl-2-(4-chlorophenyl)ethyl
-COOH	5-CH_2CH_2	-CH2COOH	2,2-diphenylvinyl
-COOH	5-CH_2CH_2	-CH_2COOH	2-phenylethyl
-COOH	5-CH_2CH_2	-CH_2COOH	2,2-diphenylethyl
-COOH	5-CH_2CH_2	-CH_2COOH	pentyl
-COOH	5-CH_2CH_2	-CH2COOH	2-naphthyl
-COOH	5-CH_2CH_2	-CH_2COOH	2-(4-methoxyphenyl)vinyl
-COOH	5-CH2CH2	-CH2COOH	2-(4-chlorophenyl)vinyl
-COOH	5-CH_2CH_2	-CH_2COOH	2-phenyl-2-(4-methoxyphenyl)vinyl
-COOH	5-CH_2CH_2	-CH_2COOH	2-phenyl-2-(4-chlorophenyl)vinyl
-COOH	5-CH_2CH_2	-CH_2COOH	2-(4-methoxyphenyl)ethyl
-COOH	5-CH_2CH_2	-CH_2COOH	2-(4-chlorophenyl)ethyl
-COOH	5-CH_2CH_2	-CH_2COOH	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	5-CH_2CH_2	-CH_2COOH	2-phenyl-2-(4-chlorophenyl)ethyl
-COOH	6-bond	hydrogen	2-phenylethyl
-COOH	6-bond	hydrogen	2,2-diphenylethyl
-COOH	6-bond	hydrogen	pentyl
-COOH	6-bond	hydrogen	2-naphthyl
-COOH	6-bond	hydrogen	2-(4-methoxyphenyl)vinyl
-COOH	6-bond	hydrogen	2-(4-chlorophenyl)vinyl
-COOH	6-bond	hydrogen	2-phenyl-2-(4-methoxyphenyl)vinyl
-COOH	6-bond	hydrogen	2-phenyl-2-(4-chlorophenyl)vinyl
-COOH	6-bond	hydrogen	2-(4-methoxyphenyl)ethyl
-COOH	6-bond	hydrogen	2-(4-chlorophenyl)ethyl
-COOH	6-bond	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	6-bond	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl
-COOH	6-CH_2CH_2	hydrogen	2-phenylethyl
-COOH	6-CH_2CH_2	hydrogen	2,2-diphenylethyl
-COOH	6-CH_2CH_2	hydrogen	pentyl
-COOH	6-CH_2CH_2	hydrogen	2-naphthyl
-COOH	6-CH_2CH_2	hydrogen	2-(4-methoxyphenyl)vinyl
-COOH	6-CH_2CH_2	hydrogen	2-(4-chlorophenyl)vinyl
-COOH	6-CH_2CH_2	hydrogen	2-phenyl-2-(4-methoxyphenyl)vinyl
-COOH	6-CH_2CH_2	hydrogen	2-phenyl-2-(4-chlorophenyl)vinyl
-COOH	6-CH_2CH_2	hydrogen	2-(4-methoxyphenyl)ethyl
-COOH	6-CH_2CH_2	hydrogen	2-(4-chlorophenyl)ethyl
-COOH	6-CH_2CH_2	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl

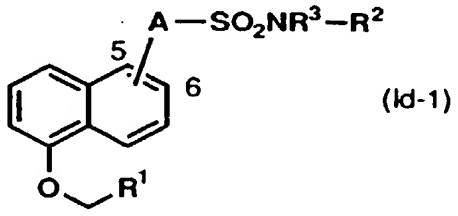
(continued)

R^1	A	R^3	R^2
-COOH	6-CH_2CH_2	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl
-$CONH_2$	5-bond	hydrogen	2-phenylvinyl
-$CONH_2$	5-bond	hydrogen	2,2-diphenylvinyl
-$CONH_2$	5-bond	hydrogen	2-phenylethyl
-$CONH_2$	5-bond	hydrogen	2,2-diphenylethyl
-$CONH_2$	5-bond	hydrogen	pentyl
-$CONH_2$	5-bond	hydrogen	2-naphthyl
-$CONH_2$	5-bond	hydrogen	2-(4-methoxyphenyl)vinyl
-$CONH_2$	5-bond	hydrogen	2-(4-chlorophenyl)vinyl
-$CONH_2$	5-bond	hydrogen	2-phenyl-2-(4-methoxyphenyl)vinyl
-$CONH_2$	5-bond	hydrogen	2-phenyl-2-(4-chlorophenyl)vinyl
-$CONH_2$	5-bond	hydrogen	2-(4-methoxyphenyl)ethyl
-$CONH_2$	5-bond	hydrogen	2-(4-chlorophenyl)ethyl
-$CONH_2$	5-bond	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
-$CONH_2$	5-bond	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2,2-diphenylvinyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2-phenylethyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2,2-diphenylethyl
-$CONH_2$	5-CH_2CH_2	hydrogen	pentyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2-naphthyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2-(4-methoxyphenyl)vinyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2-(4-chlorophenyl)vinyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2-phenyl-2-(4-methoxyphenyl)vinyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2-phenyl-2-(4-chlorophenyl)vinyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2-(4-methoxyphenyl)ethyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2-(4-chlorophenyl)ethyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl
-CH_2OH	5-bond	hydrogen	2-phenylvinyl
-CH_2OH	5-bond	hydrogen	2,2-diphenylvinyl
-CH_2OH	5-bond	hydrogen	2-phenylethyl
-CH_2OH	5-bond	hydrogen	2,2-diphenylethyl
-CH_2OH	5-bond	hydrogen	pentyl
-CH_2OH	5-bond	hydrogen	2-naphthyl
-CH_2OH	5-bond	hydrogen	2-(4-methoxyphenyl)vinyl
-CH_2OH	5-bond	hydrogen	2-(4-chlorophenyl)vinyl
-CH_2OH	5-bond	hydrogen	2-phenyl-2-(4-methoxyphenyl)vinyl
-CH_2OH	5-bond	hydrogen	2-phenyl-2-(4-chlorophenyl)vinyl

(continued)

R^1	A	R^3	R^2
$-CH_2OH$	5-bond	hydrogen	2-(4-methoxyphenyl)ethyl
$-CH_2OH$	5-bond	hydrogen	2-(4-chlorophenyl)ethyl
$-CH_2OH$	5-bond	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
$-CH_2OH$	5-bond	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2,2-diphenylvinyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-phenylethyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2,2-diphenylethyl
-CH20H	$5-CH_2CH_2$	hydrogen	pentyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-naphthyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-(4-methoxyphenyl)vinyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-(4-chlorophenyl)vinyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-phenyl-2-(4-methoxyphenyl)vinyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-phenyl-2-(4-chlorophenyl)vinyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-(4-methoxyphenyl)ethyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-(4-chlorophenyl)ethyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl

(Id-1)



(Id-1)

R^1	A	R^3	R^2
-COOH	5-bond	hydrogen	pentyl
-COOH	5-bond	hydrogen	2-naphthyl
-COOH	5-bond	hydrogen	2-(4-methoxyphenyl)ethyl
-COOH	5-bond	hydrogen	2-(4-chlorophenyl)ethyl
-COOH	5-bond	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	5-bond	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl
-COOH	5-bond	methyl	2-phenylethyl
-COOH	5-bond	methyl	2,2-diphenylethyl
-COOH	5-bond	methyl	pentyl

(continued)

R^1	A	R^3	R^2
-COOH	5-bond	methyl	2-naphthyl
-COOH	5-bond	methyl	2-(4-methoxyphenyl)ethyl
-COOH	5-bond	methyl	2-(4-chlorophenyl)ethyl
-COOH	5-bond	methyl	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	5-bond	methyl	2-phenyl-2-(4-chlorophenyl)ethyl
-COOH	5-bond	$-CH_2COOH$	2-phenylethyl
-COOH	5-bond	$-CH_2COOH$	2,2-diphenylethyl
-COOH	5-bond	$-CH_2COOH$	pentyl
-COOH	5-bond	$-CH_2COOH$	2-naphthyl
-COOH	5-bond	$-CH_2COOH$	2-(4-methoxyphenyl)ethyl
-COOH	5-bond	$-CH_2COOH$	2-(4-chlorophenyl)ethyl
-COOH	5-bond	$-CH_2COOH$	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	5-bond	$-CH_2COOH$	2-phenyl-2-(4-chlorophenyl)ethyl
-COOH	$5-CH_2CH_2$	hydrogen	pentyl
-COOH	$5-CH_2CH_2$	hydrogen	2-naphthyl
-COOH	$5-CH_2CH_2$	hydrogen	2-(4-methoxyphenyl)ethyl
-COOH	$5-CH_2CH_2$	hydrogen	2-(4-chlorophenyl)ethyl
-COOH	$5-CH_2CH_2$	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	$5-CH_2CH_2$	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl
-COOH	$5-CH_2CH_2$	methyl	2-phenylethyl
-COOH	$5-CH_2CH_2$	methyl	2,2-diphenylethyl
-COOH	$5-CH_2CH_2$	methyl	pentyl
-COOH	$5-CH_2CH_2$	methyl	2-naphthyl
-COOH	$5-CH_2CH_2$	methyl	2-(4-methoxyphenyl)ethyl
-COOH	$5-CH_2CH_2$	methyl	2-(4-chlorophenyl)ethyl
-COOH	$5-CH_2CH_2$	methyl	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	$5-CH_2CH_2$	methyl	2-phenyl-2-(4-chlorophenyl)ethyl
-COOH	$5-CH_2CH_2$	$-CH_2COOH$	2-phenylethyl
-COOH	$5-CH_2CH_2$	$-CH_2COOH$	2,2-diphenylethyl
-COOH	$5-CH_2CH_2$	$-CH_2COOH$	pentyl
-COOH	$5-CH_2CH_2$	$-CH_2COOH$	2-naphthyl
-COOH	$5-CH_2CH_2$	$-CH_2COOH$	2-(4-methoxyphenyl)ethyl
-COOH	$5-CH_2CH_2$	$-CH_2COOH$	2-(4-chlorophenyl)ethyl
-COOH	$5-CH_2CH_2$	$-CH_2COOH$	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	$5-CH_2CH_2$	$-CH_2COOH$	2-phenyl-2-(4-chlorophenyl)ethyl
-COOH	6-bond	hydrogen	2-phenylethyl
-COOH	6-bond	hydrogen	2,2-diphenylethyl
-COOH	6-bond	hydrogen	pentyl

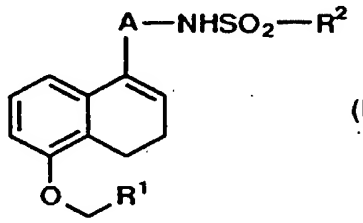
(continued)

R^1	A	R^3	R^2
-COOH	6-bond	hydrogen	2-naphthyl
-COOH	6-bond	hydrogen	2-(4-methoxyphenyl)ethyl
-COOH	6-bond	hydrogen	2-(4-chlorophenyl)ethyl
-COOH	6-bond	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	6-bond	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl
-COOH	6-CH_2CH_2	hydrogen	2-phenylethyl
-COOH	6-CH_2CH_2	hydrogen	2,2-diphenylethyl
-COOH	6-CH_2CH_2	hydrogen	pentyl
-COOH	6-CH_2CH_2	hydrogen	2-naphthyl
-COOH	6-CH_2CH_2	hydrogen	2-(4-methoxyphenyl)ethyl
-COOH	6-CH_2CH_2	hydrogen	2-(4-chlorophenyl)ethyl
-COOH	6-CH_2CH_2	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
-COOH	6-CH_2CH_2	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl
-$CONH_2$	5-bond	hydrogen	2-phenylethyl
-$CONH_2$	5-bond	hydrogen	2,2-diphenylethyl
-$CONH_2$	5-bond	hydrogen	pentyl
-CONH2	5-bond	hydrogen	2-naphthyl
-$CONH_2$	5-bond	hydrogen	2-(4-methoxyphenyl)ethyl
-$CONH_2$	5-bond	hydrogen	2-(4-chlorophenyl)ethyl
-$CONH_2$	5-bond	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
-$CONH_2$	5-bond	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl
-CONH2	5-CH_2CH_2	hydrogen	2-phenylethyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2,2-diphenylethyl
-$CONH_2$	5-CH_2CH_2	hydrogen	pentyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2-naphthyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2-(4-methoxyphenyl)ethyl
-CONH2	5-CH_2CH_2	hydrogen	2-(4-chlorophenyl)ethyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
-$CONH_2$	5-CH_2CH_2	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl
-CH_2OH	5-bond	hydrogen	2-phenylethyl
-CH_2OH	5-bond	hydrogen	2,2-diphenylethyl
-CH_2OH	5-bond	hydrogen	pentyl
-CH_2OH	5-bond	hydrogen	2-naphthyl
-CH_2OH	5-bond	hydrogen	2-(4-methoxyphenyl)ethyl
-CH_2OH	5-bond	hydrogen	2-(4-chlorophenyl)ethyl
-CH_2OH	5-bond	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
-CH_2OH	5-bond	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl
-CH_2OH	5-CH_2CH_2	hydrogen	2-phenylethyl

(continued)

R^1	A	R^3	R^2
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2,2-diphenylethyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	pentyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-naphthyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-(4-methoxyphenyl)ethyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-(4-chlorophenyl)ethyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-phenyl-2-(4-methoxyphenyl)ethyl
$-CH_2OH$	$5-CH_2CH_2$	hydrogen	2-phenyl-2-(4-chlorophenyl)ethyl

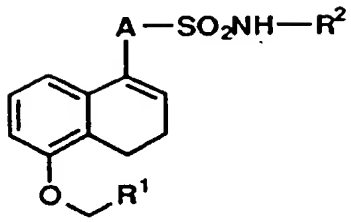
(Ia-2)



(Ia-2)

R^1	A	R^2
-COOH	bond	2,2-diphenylvinyl
-COOH	bond	2,2-diphenylethyl
-COOH	$-CH_2CH_2-$	2-phenylvinyl
-COOH	$-CH_2CH_2-$	2,2-diphenylvinyl
-COOH	$-CH_2CH_2-$	2-phenylethyl
-COOH	$-CH_2CH_2-$	2,2-diphenylethyl
$-COOH_2$	bond	2-phenylvinyl
$-COOH_2$	bond	2,2-diphenylvinyl
$-CONH_2$	bond	2-phenylethyl
$-CONH_2$	bond	2,2-diphenylethyl
$-CONH_2$	$-CH_2CH_2-$	2-phenylvinyl
$-CONH_2$	$-CH_2CH_2-$	2,2-diphenylvinyl
$-CONH_2$	$-CH_2CH_2-$	2-phenylethyl
$-CONH_2$	$-CH_2CH_2-$	2,2-diphenylethyl

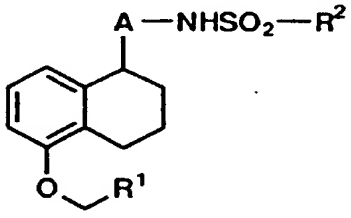
(Id-2)



(Id-2)

R^1	A	R^2
-COOH	bond	2-phenylvinyl
-COOH	bond	2,2-diphenylvinyl
-COOH	bond	2-phenylethyl
-COOH	bond	2,2-diphenylethyl
-COOH	$-CH_2CH_2-$	2-phenylvinyl
-COOH	$-CH_2CH_2-$	2,2-diphenylviny
-COOH	$-CH_2CH_2-$	2-phenylethyl
-COOH	$-CH_2CH_2-$	2,2-diphenylethyl
$-CONH_2$	bond	2-phenylvinyl
$-CONH_2$	bond	2,2-diphenylvinyl
$-CONH_2$	bond	2-phenylethyl
$-CONH_2$	bond	2,2-diphenylethyl
$-CONH_2$	$-CH_2CH_2-$	2-phenylvinyl
$-CONH_2$	$-CH_2CH_2-$	2,2-diphenylvinyl
$-CONH_2$	$-CH_2CH_2-$	2-phenylethyl
$-CONH_2$	$-CH_2CH_2-$	2,2-diphenylethyl

(Ia-3)



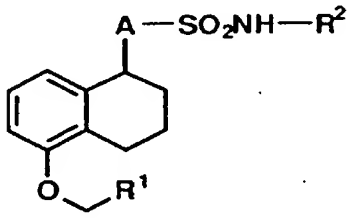
(Ia-3)

R^1	A	R^2
-COOH	bond	2-phenylethyl
-COOH	bond	2,2-diphenylethyl
-COOH	$-CH_2CH_2-$	2,2-diphenylvinyl
-COOH	$-CH_2CH_2-$	2-phenylethyl

(continued)

R^1	A	R^2
-COOH	$-CH_2CH_2-$	2,2-diphenylethyl
$-CONH_2$	bond	2-phenylvinyl
-CONH2	bond	2,2-diphenylvinyl
-CONH2	bond	2-phenylethyl
-CONH2	bond	2,2-diphenylethyl
$-CONH_2$	$-CH_2CH_2-$	2-phenylvinyl
-CONH2	$-CH_2CH_2-$	2,2-diphenylvinyl
-CONH2	$-CH_2CH_2-$	2-phenylethyl
-CONH2	$-CH_2CH_2-$	2,2-diphenylethyl

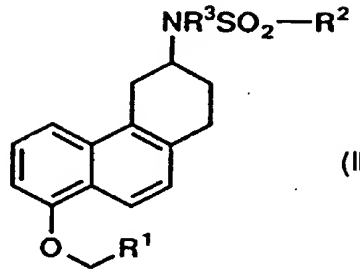
(Id-3)



(Id-3)

R^1	A	R^2
-COOH	bond	2-phenylvinyl
-COOH	bond	2,2-diphenylvinyl
-COOH	bond	2-phenylethyl
-COOH	bond	2,2-diphenylethyl
-COOH	$-CH_2CH_2-$	2-phenylvinyl
-COOH	$-CH_2CH_2-$	2,2-diphenylvinyl
-COOH	$-CH_2CH_2-$	2-phenylethyl
-COOH	$-CH_2CH_2-$	2,2-diphenylethyl
$-CONH_2$	bond	2-phenylvinyl
$-CONH_2$	bond	2,2-diphenylvinyl
$-CONH_2$	bond	2-phenylethyl
$-CONH_2$	bond	2,2-diphenylethyl
$-CONH_2$	$-CH_2CH_2-$	2-phenylvinyl
$-CONH_2$	$-CH_2CH_2-$	2,2-diphenylvinyl
$-CONH_2$	$-CH_2CH_2-$	2-phenylethyl
$-CONH_2$	$-CH_2CH_2-$	2,2-diphenylethyl

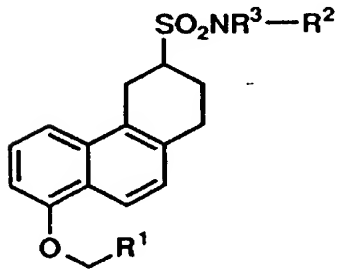
(Ib-1)



(Ib-1)

R^1	R^3	R^2
-COOH	hydrogen	2,2-diphenylvinyl
-COOH	hydrogen	2-phenylethyl
-COOH	hydrogen	2,2-diphenylethyl
-COOH	methyl	2-phenylvinyl
-COOH	methyl	2,2-diphenylvinyl
-COOH	methyl	2-phenylethyl
-COOH	methyl	2,2-diphenylethyl
-COOH	$-CH_2COOH$	2-phenylvinyl
-COOH	$-CH_2COOH$	2,2-diphenylvinyl
-COOH	$-CH_2COOH$	2-phenylethyl
-COOH	$-CH_2COOH$	2,2-diphenylethyl
$-CONH_2$	hydrogen	2-phenylvinyl
$-CONH_2$	hydrogen	2,2-diphenylvinyl
$-CONH_2$	hydrogen	2-phenylethyl
$-CONH_2$	hydrogen	2,2-diphenylethyl
$-CH_2OH$	hydrogen	2-phenylvinyl
$-CH_2OH$	hydrogen	2,2-diphenylvinyl
$-CH_2OH$	hydrogen	2-phenylethyl
$-CH_2OH$	hydrogen	2,2-diphenylethyl

(Ie-1)



(Ie-1)

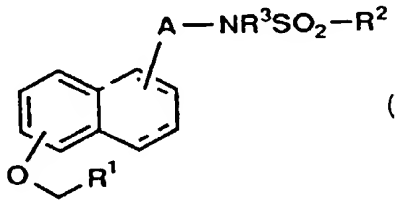
R^1	R^3	R^2
-COOH	hydrogen	2-phenylvinyl
-COOH	hydrogen	2,2-diphenylvinyl
-COOH	hydrogen	2-phenylethyl
-COOH	methyl	2-phenylvinyl
-COOH	methyl	2,2-diphenylvinyl
-COOH	methyl	2-phenylethyl
-COOH	methyl	2,2-diphenylethyl
-COOH	$-CH_2COOH$	2-phenylvinyl
-COOH	$-CH_2COOH$	2,2-diphenylvinyl
-COOH	$-CH_2COOH$	2-phenylethyl
-COOH	$-CH_2COOH$	2,2-diphenylethyl
$-CONH_2$	hydrogen	2-phenylvinyl
$-CONH_2$	hydrogen	2,2-diphenylvinyl
$-CONH_2$	hydrogen	2-phenylethyl
$-CONH_2$	hydrogen	2,2-diphenylethyl
$-CH_2OH$	hydrogen	2-phenylvinyl
$-CH_2OH$	hydrogen	2,2-diphenylvinyl
$-CH_2OH$	hydrogen	2-phenylethyl
$-CH_2OH$	hydrogen	2,2-diphenylethyl

Salts

The compounds of the present invention of the formula (I) may be converted into the corresponding salts. Non-toxic and water-soluble salts are preferable. Suitable salts include: salts of alkali metals (e.g. sodium and potassium), salts of alkaline earth metals (e.g. calcium and magnesium), ammonium salts, salts of pharmaceutically acceptable organic amines (e.g. tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)aminomethane, lysine, arginine and N-methyl-D-glucamine).

The compounds of the formula (I) may be converted into the corresponding acid addition salts. Non-toxic and water-soluble salts are preferable. Suitable salts include:
salts of inorganic acids, e.g. the hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate and nitrate; and salts of organic acids, e.g. the acetate, lactate, tartarate, benzoate, citrate, methanesulphonate, ethanesulphonate, benzenesulphonate, toluenesulphonate, isethioate, glucuronate and gluconate.

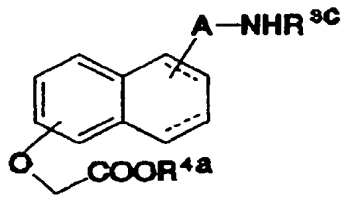
(1) According to a feature of the present invention compounds of formula (I) which conform to the formula (Ia):



(Ia)

wherein all the symbols are as hereinbefore defined, in the compounds of the formula (I), may be prepared:

(i) by reacting a compound of the formula (II):

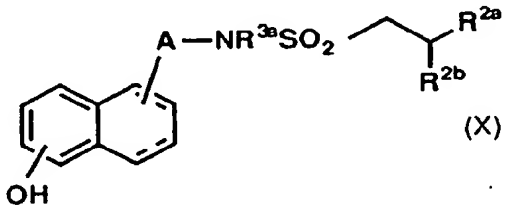


(II)

wherein R^{3c} is hydrogen, C1-4 alkyl or $-CH_2COOR^{4a}$, in which R^{4a} is C1-4 alkyl and the other symbols are as hereinbefore defined, with a compound of the formula (III):

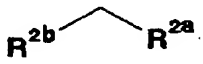
$$X^1SO_2\text{-}R^2 \qquad \text{(III)}$$

wherein X^1 is halogen and the other symbols are as hereinbefore defined, or
(ii) by reacting a compound of the formula (X):



(X)

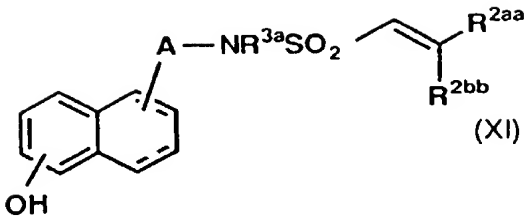
wherein



is (i) C1-5 alkyl, C2-5 alkenyl or C3-5 alkynyl,

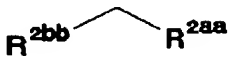
or (ii) C1-5 alkyl, C2-5 alkenyl or C3-5 alkynyl substituted by one, two or three substituents selected from phenyl, C4-7 cycloalkyl or phenyl substituted by one, two or three substituents selected from C1-4 alkyl, C1-4 alkoxy or halogen
R^{3a} is hydrogen or C1-4 alkyl,

and the other symbols are as hereinbefore defined,
or a compound of the formula (XI):



(XI)

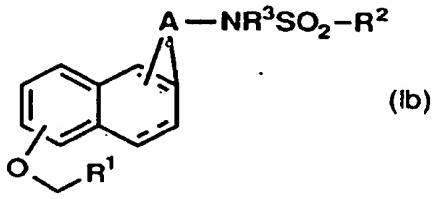
wherein



is (i) C1-5 alkyl, or
(ii) C1-5 alkyl substituted by one, two or three substituents selected from phenyl, C4-7 cycloalkyl or phenyl substituted by one, two or three substituents selected from C1-4 alkyl, C1-4 alkoxy or halogen
and the other symbols are as hereinbefore defined,
with a compound of the formula (VI):

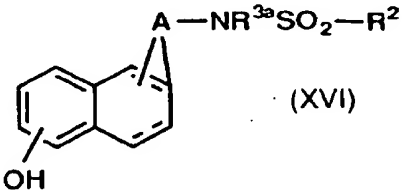
(VI)

wherein X^3 is halogen and the other symbols are as hereinbefore defined,
optionally followed by the conversion of a group $COOR^{4a}$ in a compound thus obtained into a group COOH, $CONR^5R^6$ or CH_2OH.
(2) According to a further feature of the present invention compounds of formula (I) which conform to the formula (Ib):



(Ib)

wherein all the symbols are as hereinbefore defined, may be prepared by reacting a compound of the formula (XVI):

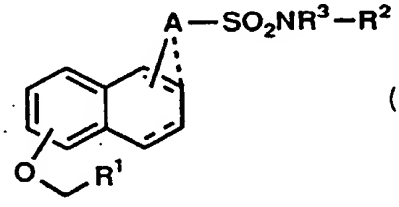


(XVI)

wherein all the symbols are as hereinbefore defined, with a compound of the formula (VI):

wherein all the symbols are as hereinbefore defined, optionally followed by the conversion of a group $COOR^{4a}$ in a compound thus obtained into a group COOH, $CONR^5R^6$ or CH_2OH.

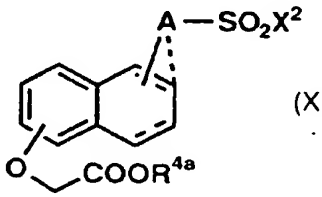
(3) According to a further feature of the present invention compounds of formula (I) which conform to formula (Ic) :



(Ic)

wherein all the symbols are as hereinbefore defined, may be prepared:

(i) by subjecting a compound of the formula (XXIII):



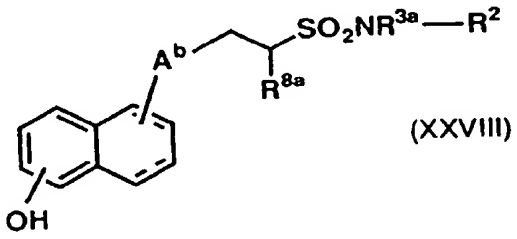
(XXIII)

wherein X^2 is halogen and the other symbols are as hereinbefore defined, with a compound of the formula (XXIV):

$$R^3HN\text{-}R^2 \qquad \text{(XXIV)}$$

wherein all the symbols are as hereinbefore defined, or

(ii) by reacting a compound of the formula (XXVIII):

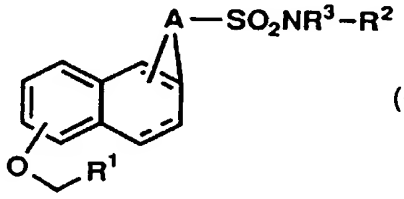


(XXVIII)

wherein A^b is a bond or C1-2 alkylene, R^{8a} is hydrogen or C1-2 alkyl and the other symbols are as hereinbefore defined, with a compound of the formula (VI):

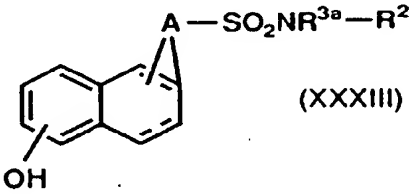
wherein all the symbols are as hereinbefore defined, optionally followed by the conversion of a group $COOR^{4a}$ in a compound thus obtained into a group COOH, $CONR^5R^6$ or CH_2OH.

(4) According to a further feature of the present invention compounds of formula (I) which conform to the formula (Ie):



(Ie)

wherein all the symbols are as hereinbefore defined,
may be prepared by reacting a compound of the formula (XXXIII):



(XXXIII)

wherein all the symbols are as hereinbefore defined,
with a compound of the formula (VI):

wherein all the symbols are as hereinbefore defined, optionally followed by the conversion of a group $COOR^{4a}$ in a compound thus obtained into a group COOH, $CONR^5R^6$ or CH_2OH.

The reaction to form a group NR^3SO_2 or SO_2NR^3 and to form a group $CONR^5R^6$ is known: for example, it may be carried out in organic solvent (e.g. benzene, toluene or methylene chloride), or in the absence of solvent, using tertiary amine (e.g. pyridine or triethylamine) at 0-50°C, or it may be carried out in organic solvent (e.g. methylene chloride or tetrahydrofuran(THF)), using a corresponding base, in the presence or absence of a corresponding condensing agents (e.g. 2-chloro-N-methylpyridinium iodide) at 0-40°C.

The hydrolysis of an ester to a group COOH may be carried out under alkaline conditions and is known: for example, it may be carried out in a water-miscible organic solvent (e.g. methanol, ethanol dimethoxyethane or a mixture thereof), using an alkali (e.g. sodium hydroxide or potassium hydroxide), at 0-50°C.

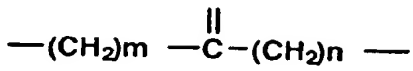
The reduction reaction to obtain a group CH_2OH from a group $COOR^7$ is known: for example, it may be carried out in organic solvent (e.g. methanol, ethanol, tetrahydrofuran or methylene chloride), using lithium aluminum hydride or sodium borohydride at 0-50°C.

The reactions (1)-(ii), (2), (3)-(ii) and (4) are known: for example, they may be carried out in an organic solvent (e. g. dimethylformamide (DMF) or acetone), in the presence of potassium carbonate or sodium carbonate at 0-160°C.

The compounds of the formula (II), (X), (XI), (XVI), (XXIII), (XXVIII) and (XXXIII) may be prepared by using the reaction depicted in the following schemes (A), (B), (C), (D), (E) and (F).

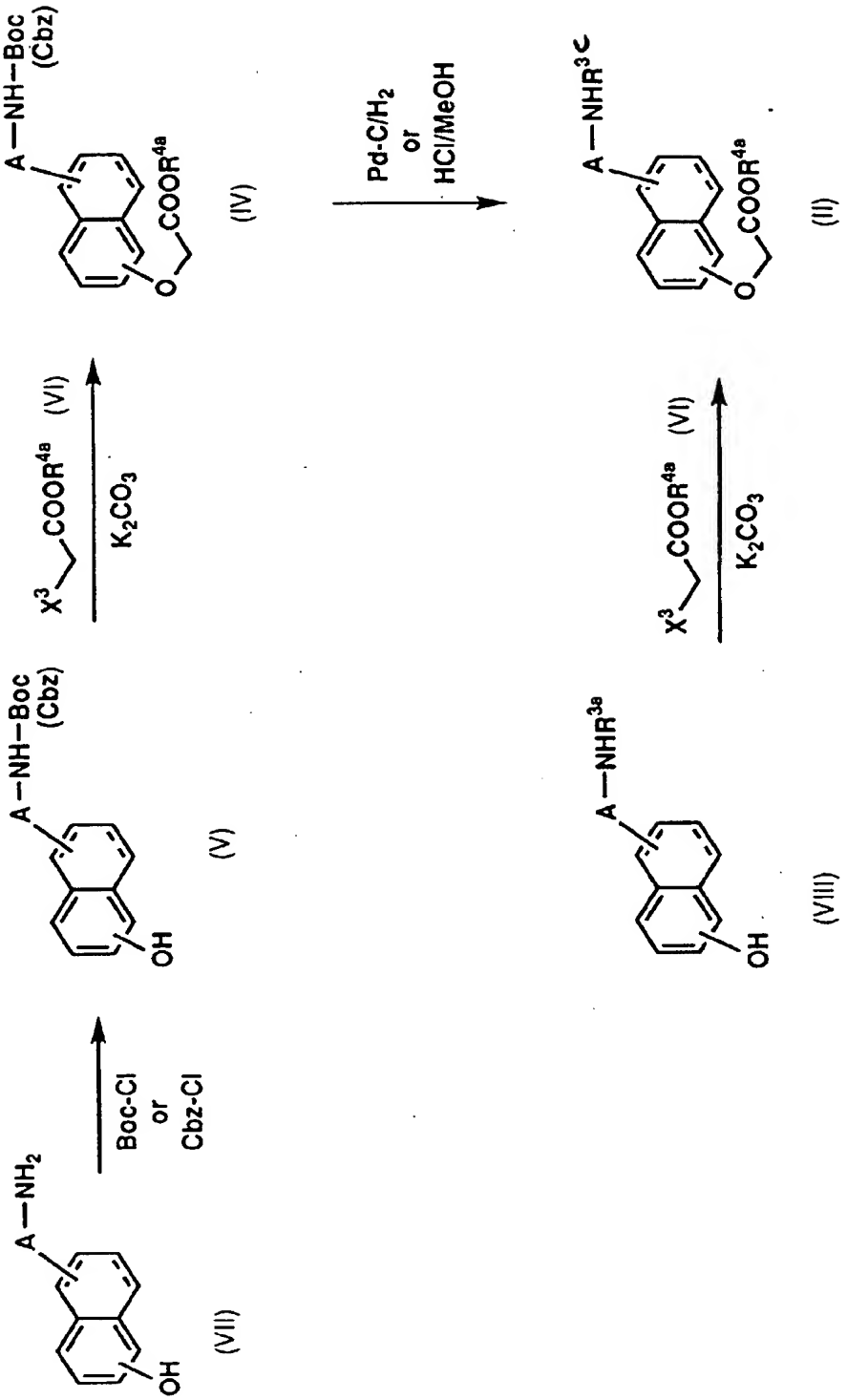
The symbols have the following meanings or are as hereinbefore defined.

Boc :	t-butoxycarbonyl
Cbz :	: benzyloxycarbonyl
TMEDA :	N, N, N', N'-tetramethylethylenediamine
X^4 :	halogen
R^{3b} :	C1-4 alkyl
A^a	

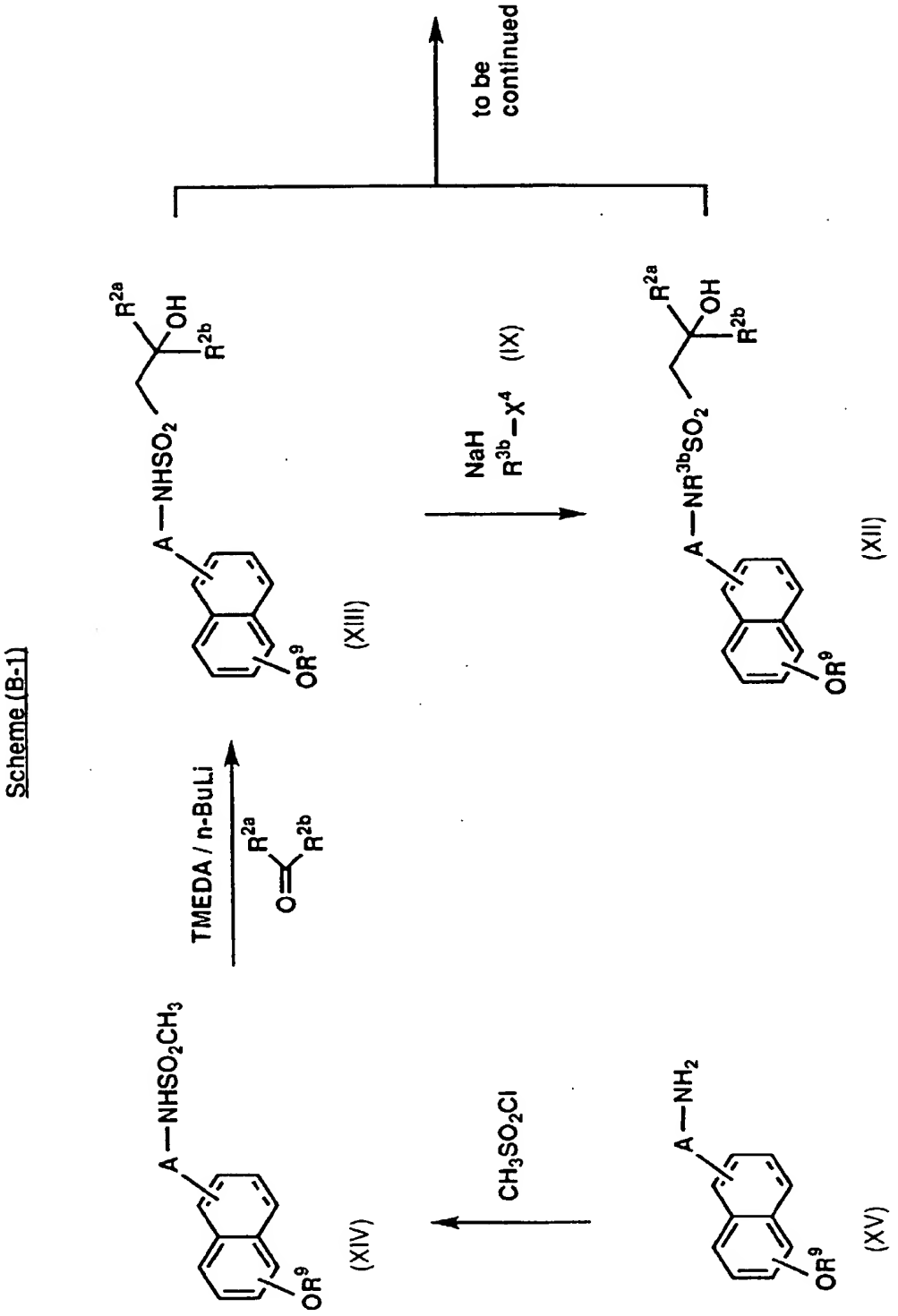


R^8:	: C1-3 alkyl
R^9 :	methyl, ethyl, methoxymethyl, tetrahydropyran

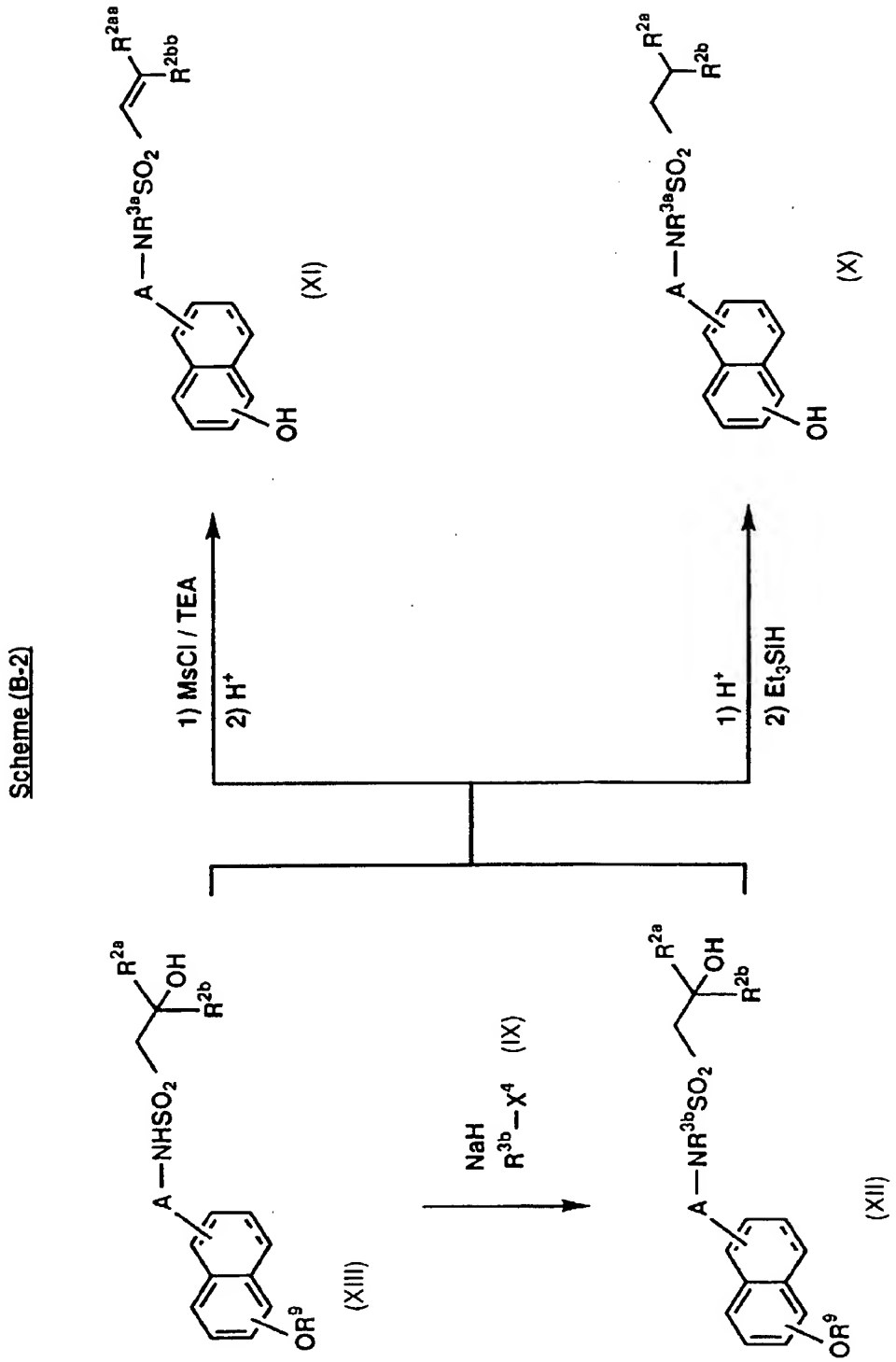
Scheme (A)


A—NH—Boc (Cbz)
COOR4a
(IV)
Pd-C/H2 or HCl/MeOH
A—NHR3c
(II)
X3—COOR4a (VI)
K2CO3
A—NH—Boc (Cbz)
OH
(V)
Boc-Cl or Cbz-Cl
A—NH2
(VII)
A—NHR3a
(VIII)

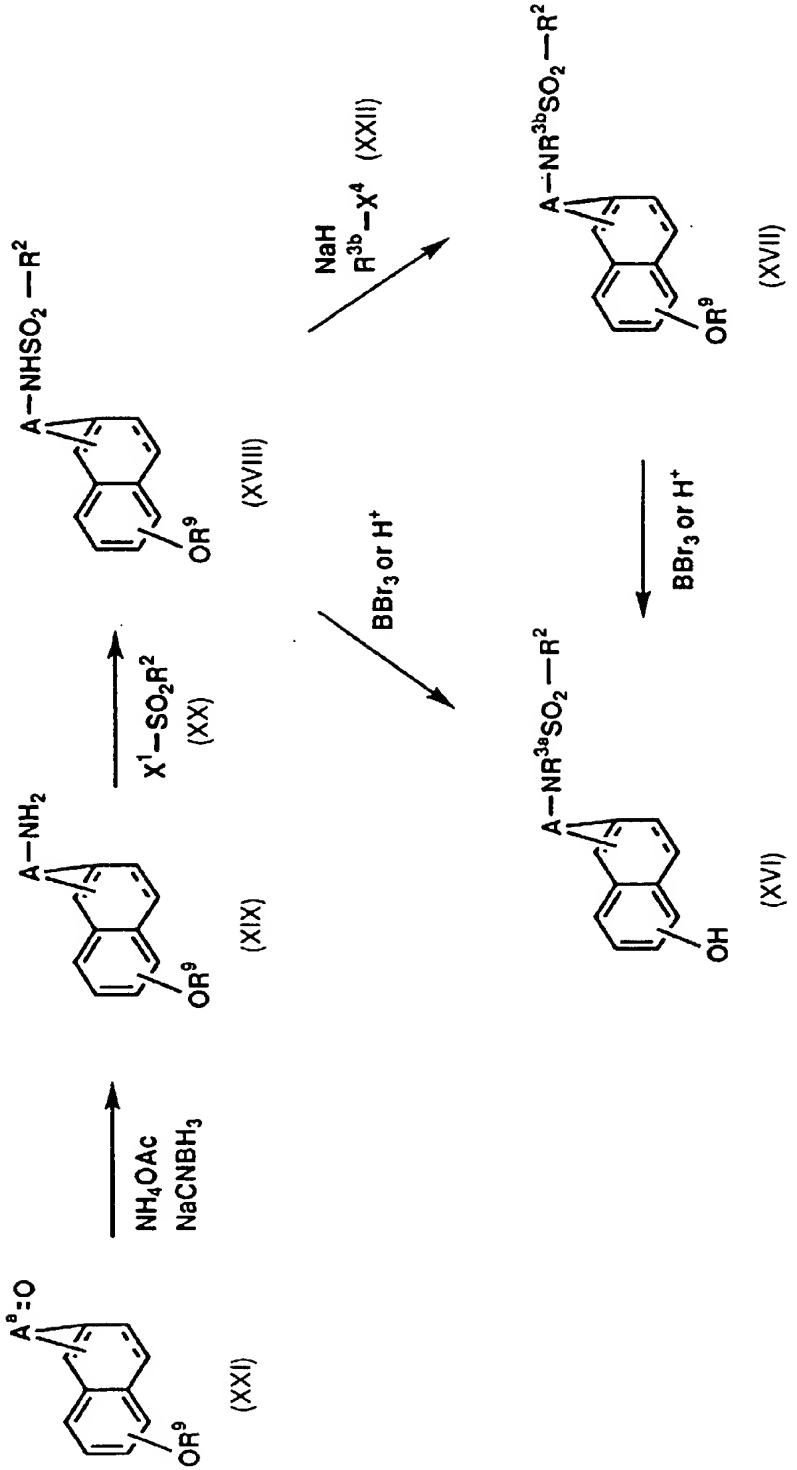
Scheme (B-1)


to be continued
NaH
$R^{3b}-X^4$ (IX)
TMEDA / n-BuLi
CH_3SO_2Cl
(XIII)
(XII)
(XIV)
(XV)

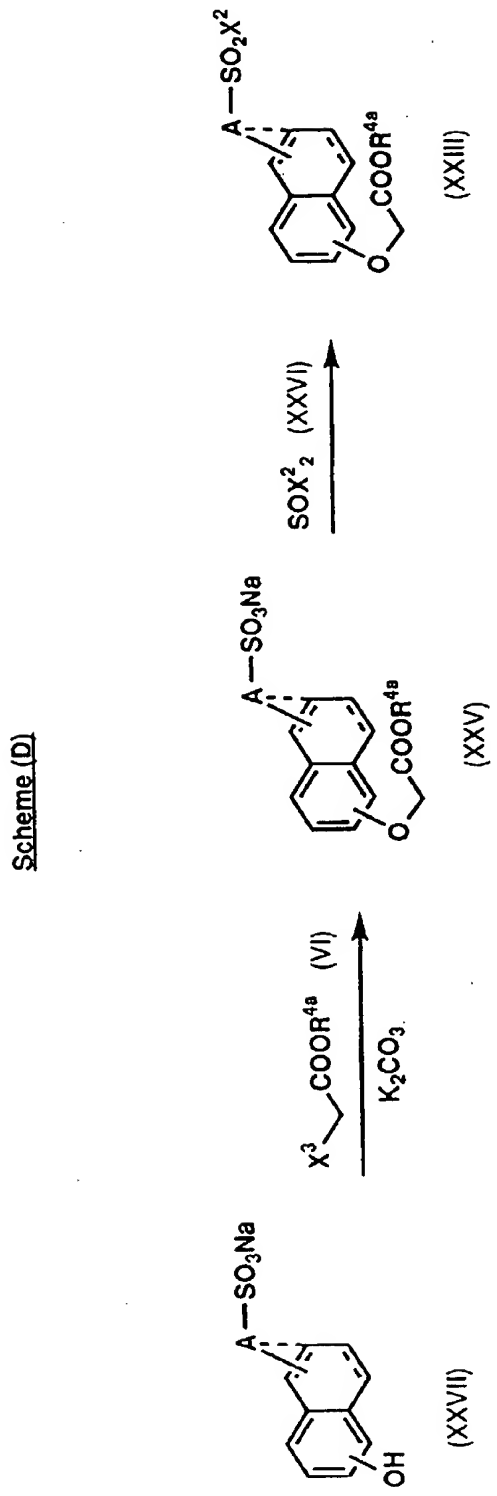
Scheme (B-2)



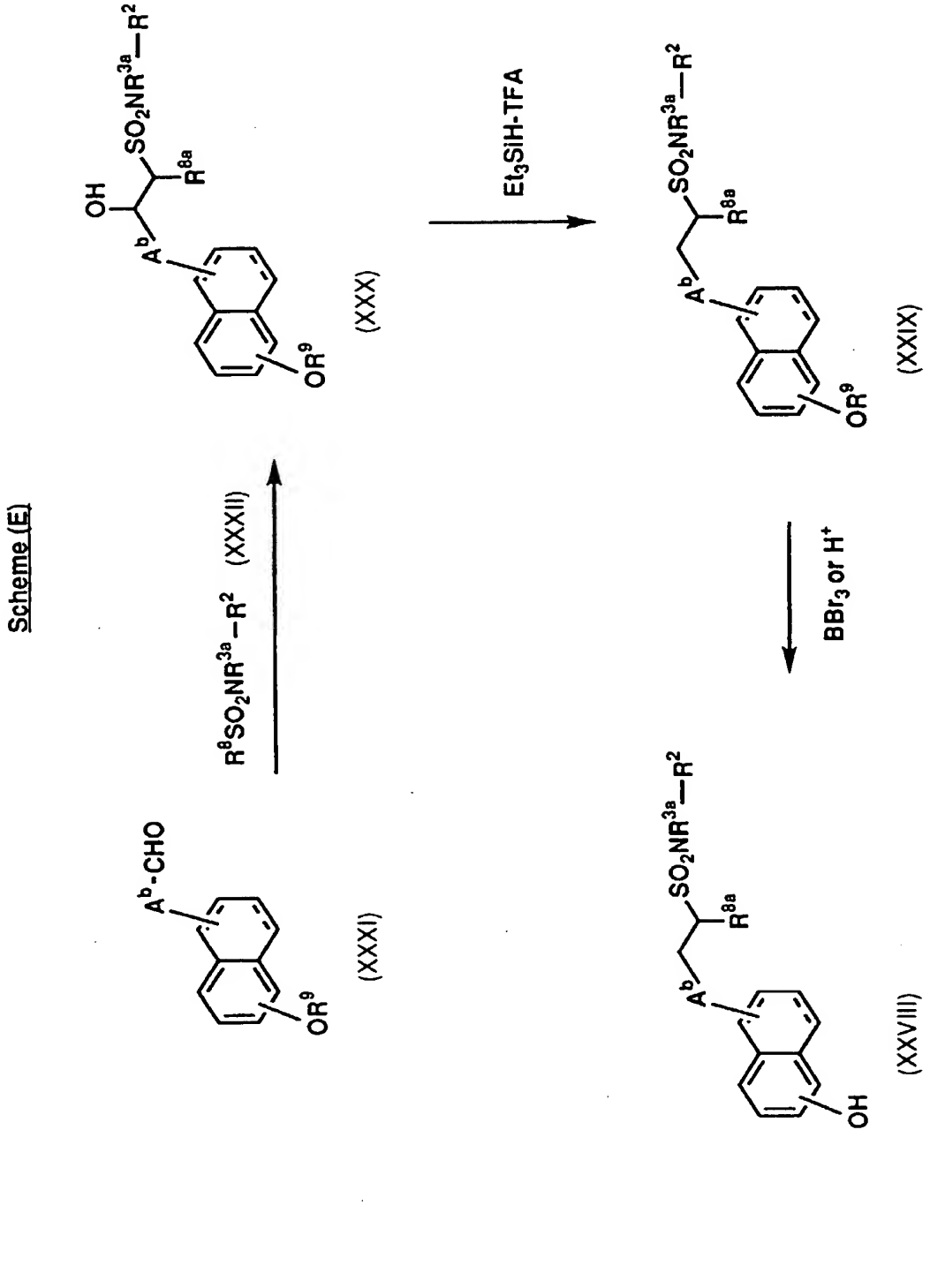
Scheme (C)


A8=O
OR9
(XXI)
NH4OAc
NaCNBH3
A—NH2
OR9
(XIX)
X1—SO2R2
(XX)
A—NHSO2—R2
OR9
(XVIII)
NaH
R3b—X4 (XXII)
A—NR3bSO2—R2
OR9
(XVII)
BBr3 or H+
BBr3 or H+
A—NR3aSO2—R2
OH
(XVI)

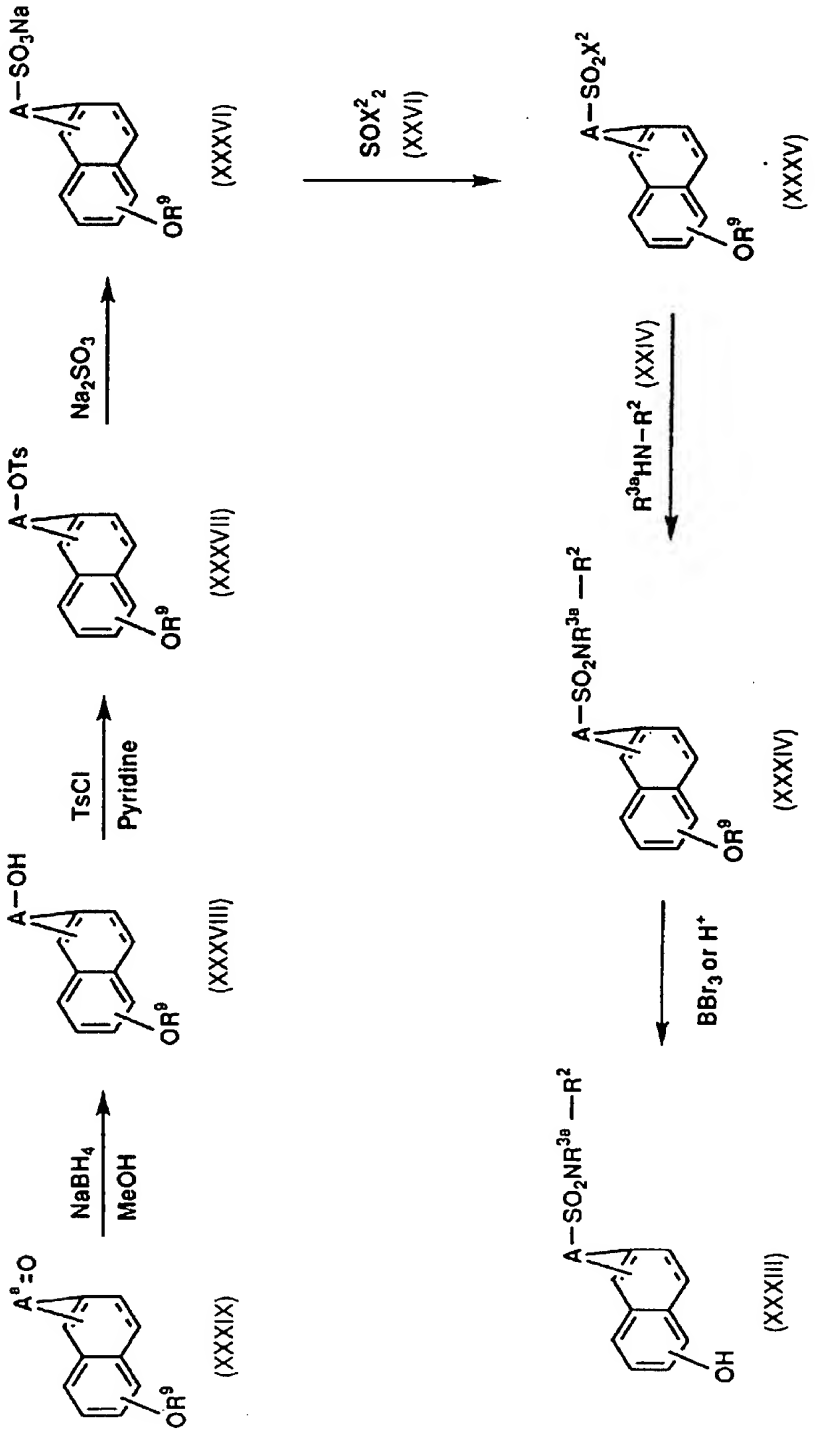
Scheme (D)


A—SO3Na
OH
(XXVII)
X3—COOR4a (VI)
K2CO3
A—SO3Na
O—COOR4a
(XXV)
SOX2 2 (XXVI)
A—SO2X2
O—COOR4a
(XXIII)

Scheme (E)



Scheme (F)


A=O
OR9
(XXXIX)
NaBH4
MeOH
A—OH
OR9
(XXXVIII)
TsCl
Pyridine
A—OTs
OR9
(XXXVII)
Na2SO3
A—SO3Na
OR9
(XXXVI)
SOX2 2
(XXVI)
A—SO2X2
OR9
(XXXV)
R3aHN—R2 (XXIV)
A—SO2NR3a—R2
OR9
(XXXIV)
BBr3 or H+
A—SO2NR3a—R2
OH
(XXXIII)

In each reaction in the present specification, products may be purified in conventional manner. For example, purification may be carried out by distillation at atmospheric or reduced pressure, high performance liquid chromatography, thin layer chromatography or column chromatography using silica gel or magnesium silicate, washing or recrystallization. Purification may be carried out after each reaction, or after a series of reactions.

The starting materials and reagents in the present invention are known per se or may be prepared by known methods.

In standard laboratory test, the activities of the compounds of formula (I) were confirmed by (i) binding assay using expression cell of the prostanoide receptor subtype.

The compounds of the present invention of the formula (I) are useful as PGE_2 antagonists or agonists, because they bind onto prostaglandin E_2 receptors and have antagonist or agonist activity on their action.

PGE_2 antagonists are expected e.g. to inhibit uterine contraction, to have an analgetic action, to inhibit digestive peristalsis or to induce sleep. Therefore, PGE_2 antagonists are considered to be useful e.g. for the prevention of abortion, as analgesics, as antidiarrheals or as sleep inducers.

PGE^2 agonists are expected to cause uterine contraction, to promote digestive peristalsis, to suppress gastric acid secretion, or to lower blood pressure. Therefore, PGE^2 agonists are considered to be useful as abortifacients, cathartics, and as antiulcer, anti-gastritis, antihypertensive agents.

(i) Binding assay using expression cell of the prostanoide receptor subtype

The preparation of membrane fraction was carried out according to the method of Sugimoto et al [J. Biol. Chem. 267, 6463-6466(1992)], using prostanoide receptor subtype (mouse $EP_{3\alpha}$).

The standard assay mixture contained membrane fraction (0.5mg/ml), [^{3}H]-PGE_2 in a final volume of 200ml was incubated for 1 hour at room temperature. The reaction was terminated by addition of 3 ml of ice-cold buffer. The mixture was rapidly filtered through a Whatman GF/B glass filter. The radioactivity associated with the filter was measured in ACS II (Amarsham) by liquid scintillation counting.

Kd and Bmax values were determined from Scatchard plots [Ann. N.Y. Acad. Sci., 51, 660(1949)]. Non-specific binding was calculated as the bond in the presence of an excess (2.5mM) of unlabeled PGE_2. In the experiment for competition of specific [^{3}H]-PGE_2 binding by the compounds of the present invention, [^{3}H]-PGE_2 was added at a concentration of 2.5nM and the compounds of the present invention were at a concentration of 1mM.

The following buffer was used in all reactions.

Buffer : 10mM potassium phosphate (pH6.0), 1mM EDTA, 10mM $MgCl_2$, 0.1M NaCl

The dissociation constant (Ki) of each compound was calculated by the following equation.

$$Ki = IC_{50}/(1+([C]/Kd))$$

Results are shown in table 1.

Table 1

Ex. No.	Ki (μm)
3(g)	0.007
3(h)	0.037
3(i)	0.037
3(p)	0.036
3(q)	0.32
3(v)	0.017
3(w)	0.028
3(aa)	0.0079
3(ff)	0.0025
6(f)	0.0075

The toxicity of the compounds of the present invention of formula (I) are very low and therefore, they may be considered safe for pharmaceutical use.

The compounds of the present invention of the formula (I) and non-toxic salts thereof, are useful as PGE_2 antagonists or agonists, because they bind onto prostaglandin E2 receptors and have an antagonist or agonist activity on

them.

PGE_2 antagonists are considered e.g. to inhibit uterine contraction, to have an analgetic action, to inhibit digestive peristalsis or to induce sleep, therefore they are useful for prevention and/or treatment of abortion, pain, diarrhea or insomnia.

PGE_2 agonists are considered to cause e.g. uterine contraction, to promote digestive peristalsis, to suppress gastric acid secretion or to lower blood pressure; therefore they are useful e.g. for prevention and/or treatment of constipation, ulcers, gastritis, as hypertensives, and for the induction of labour in pregnant female mammals.

For the purpose above described, the compounds of the formula (I), of the present invention and non-toxic salts thereof may normally be administered systemically or locally usually by oral or parenteral administration.

The present invention provides pharmaceutical compositions which comprise a naphthyloxyacetic acid derivative of formula (I) or a non-toxic salt thereof in association with a pharmaceutically acceptable carrier or coating.

The dose to be administered is determined depending upon e.g. age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment. In the human adult, the doses per person per dose are generally between 1 μg and 100 mg, by oral administration up to several times per day, and between 0.1 μg and 10 mg, by parenteral administration up to several times per day. As mentioned above, the doses to be used depend upon various conditions. Therefore, there may be cases in which doses lower than or greater than the ranges specified above may be used.

Solid compositions according to the present invention for oral administration include compressed tablets, dispersible powders and granules. In such solid compositions, one or more of the active compound(s) is or are, admixed with at least one inert diluent such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone or magnesium metasilicate aluminate. The compositions may also comprise, as is normal practice, additional substances other than inert diluents e.g. lubricating agents such as magnesium stearate, disintegrating agents such as cellulose calcium glycolate, stabilizing agent e.g. lactose and agents to assist dissolution e.g. arginine, glutamic acid or aspartic acid. The tablets or pills may, if desired, be made into gastric film-coated or enteric film-coated tablets or pills, such as sugar-coated, gelatin-coated, hydroxypropyl cellulose-coated or hydroxypropylmethyl cellulose phthalate-coated tablets or pills; two or more layers may be used. The compositions for oral administration also include capsules of absorbable material such as gelatin.

Liquid compositions for oral administration include pharmaceutically-acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as distilled water or ethanol. Besides inert diluents such compositions may also comprise adjuvants such as wetting and suspending agents, and sweetening, flavouring, perfuming and preserving agents.

Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s).

Preparations for injection according to the present invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions or emulsions. Example of aqueous solvents or suspending media are distilled water for injection and physiological salt solution. Examples of non-aqueous solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethanol, POLYSORBATE 80 (registered Trade Mark). These compositions may also include adjuvants such as preserving, wetting, emulsifying, dispersing agents, stabilizing agents (e.g. lactose) and agents to assist dissolution (e.g. arginine, glutamic acid or aspartic acid). They may also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

Other compositions for parenteral administration include liquids for external use, and endermic liniments such as ointments, suppositories for rectal administration and pessaries for vaginal administration which comprise one or more of the active compound(s) and may be prepared by known methods.

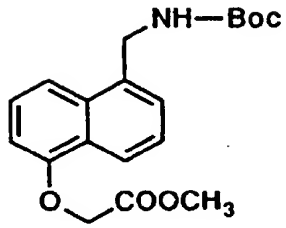
Reference examples and Examples

The following reference examples and examples illustrate the present invention.

The solvents in parentheses show the developing or eluting solvents and the ratios of the solvents used are by volume in chromatographic separations.

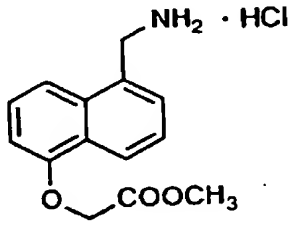
Unless otherwise specified, "NMR" spectra were measured in a chloroform-d ($CDCl_3$) solution.

Reference example 1



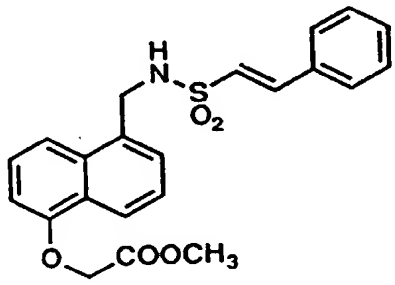
The mixture of 5-t-Butoxycarbonylaminomethyl-1- naphthol (940mg), potassium carbonate (709mg), methyl bromoacetate (0.44ml) and acetone (15 ml) was stirred overnight at room temperature. To the reaction mixture, ethyl acetate was added. The mixture was filtered and the filtrate was concentrated. The residue was purified on silica gel chromatography to give the title compound (1.20g) having the following physical data. mp:109-110°C
NMR: δ 8.34 (1H, m), 7.67 (1H, d), 7.50-7.36 (3H, m), 6.74 (1H, d), 4.90-4.63 (5H, m), 3.82 (3H,s), 1.45 (9H,s).

Reference example 2



To a solution of the compound prepared in reference example 1 (200mg) in methylene chloride (5ml), 4N hydrochloric acid / ethyl acetate (5ml) was added. The mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated to give the title compound.

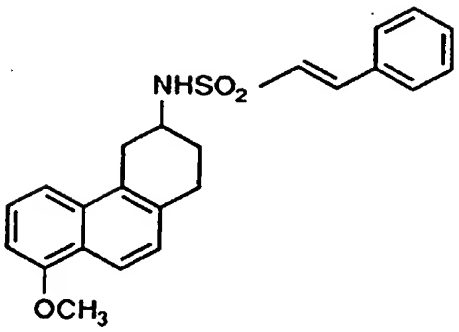
Example 1



To the compound prepared in reference example 2 (150mg), methylene chloride (10ml), pyridine (0.24ml), triethylamine (0.01ml) and 2-phenylvinylsulphonylchloride (192mg) was added. The mixture was stirred for 4 hours at room temperature. The reaction mixture was poured into water. The mixture was extracted with ethyl acetate. The organic layer was washed water and a saturated aqueous solution of sodium chloride, and dried over magnesium sulfate and concentrated. The residue was purified on silica gel chromatography to give the title compound (87mg) having the following physical data.

appearance: white solid
mp: 117-119°C
NMR: δ 8.36(1H, d), 7.68(1H, d), 7.53-7.30(9H, m), 6.74(1H, d), 6.61(1H, d), 4.79(2H, s), 4.67(3H, s), 3.83(3H, s).

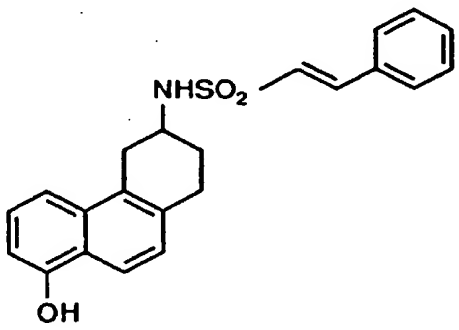
Reference example 3



To a suspension of 6-keto-1-methoxy-5,6,7,8-tetrahydrophenanthrene (1.00g) in methanol (30ml), molecular sieves 4A (1g), ammonium acetate (3.41g) and sodium cyanoborohydride (292 mg) were added. The mixture was stirred for 5 hours at room temperature. The reaction mixture was filtered, and a filtrate was concentrated. To the residue, an aqueous solution of sodium hydroxide. The mixture was extracted with ethyl acetate. The organic layer was dried over potassium carbonate, and concentrated. The residue was dissolved into ethyl acetate and 4N hydrochloric acid/ethyl acetate was added to it. The precipitated crystals was collected and dried, and 6-amine-1-methoxy-5,6,7,8-tetrahydrophenanthrene hydrochloride (1.0g) was obtained.

To a solution of the above compound (500mg) in methylene chloride (5ml), triethylamine (1ml) and b-styrylsulfonamide (606mg) was added at 0iC. The mixture was stirred for 30 minutes at room temperature. The reaction mixture was poured into an aqueous solution of hydrochloric acid. The mixture was extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous solution of sodium chloride, and dried over and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3:1) to give the title compound (331mg) having the following physical data.
TLC: Rf 0.55 (hexane : ethyl acetate = 1:1)

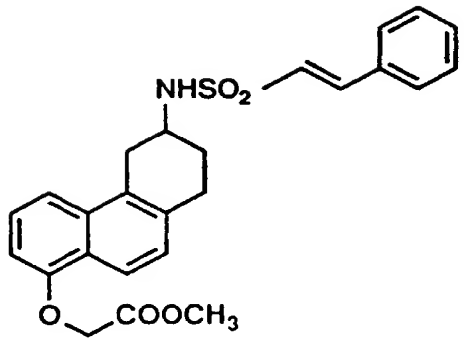
Reference example 4



To a solution of the compound prepared in reference example 3 (300mg) in methylene chloride (4 ml), a solution of boron tribromide (0.22ml) in methylene chloride (2ml) was added at -20°C. The mixture was stirred for 2 hours at -20-0°C. The reaction mixture was poured into ice water, and extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous solution of sodium chloride, and dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3:2) to give the title compound (282mg) having the following physical data.

TLC: Rf 0.39 (hexane : ethyl acetate = 1:1)

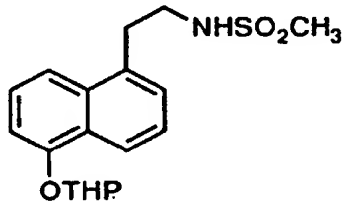
Example 2



A solution of the compound prepared in reference example 4 (150mg), methyl bromoacetate (0.056ml), sodium carbonate (85mg) in dimethylformamide (DMF; 3 ml) was stirred for 4.5 hours at 100°C. The reaction mixture was cooled, and poured into water and extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous solution of sodium chloride, and dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate : benzene = 1:9) to give the title compound (142mg) having the following physical data.

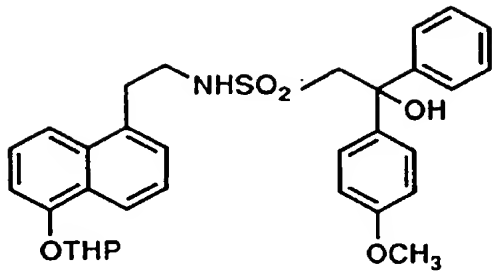
TLC: Rf 0.35 (15% ethyl acetate/ benzene)
NMR: δ 8.17 (1H, d), 7.85-7.16 (9H, m), 6.80 (1H, d), 6.68 (1H, d), 4.79 (2H, s), 4.58 (1H, d), 4.00-3.75 (4H, m), 3.49 (1H, dd), 3.10-2.93 (3H, m), 2.25-2.08 (1H, m), 2.03-1.80 (1H, m).

Reference example 5



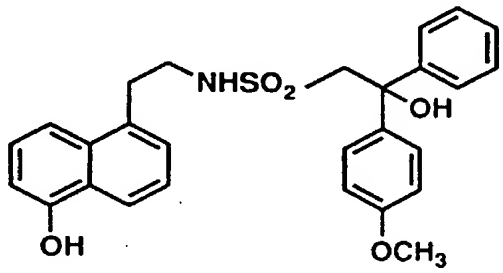
To a solution of 5-(2-aminoethyl)-1-tetrahydropyranyloxynaphthalene (3.0g) in methylene chloride (15 ml), triethylamine (2.81ml) and mesyl chloride (1.35ml) was added at 0°C. The mixture was stirred for 1 hours at room temperature. The reaction mixture was poured into dil. hydrochloric acid. The mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride, and dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate : hexane = 1 : 2) to give the title compound (2.20g) having the following physical data.
TLC: Rf 0.42 (hexane : ethyl acetate = 1:1)

Reference example 6



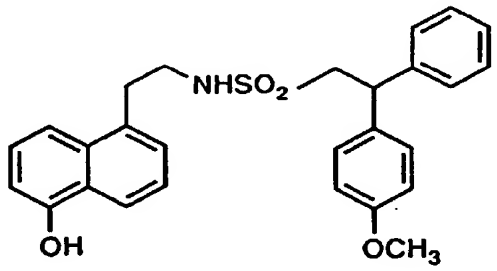
A solution of the compound prepared in reference example 5 (300mg) in THF (5 ml), tetramethylethlenediamine (TMEDA; 0.26ml) was added. The mixture was cooled at -60°C under an atmosphere of argon. To the mixture, n-butyl lithium (1.66M in hexane; 1.60ml) was dropped. The mixture was warmed to -30°C for 1.5 hours. The reaction mixture was recooled at -60°C. A solution of p-methoxybenzophenone (200mg) in THF (3ml) was added to the above mixture. The mixture was warmed to -30°C with stirring. Water was poured into the reaction mixture. The mixture was extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous solution of sodium chloride, and dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3:1) to give the title compound (253mg) having the following physical data.
TLC: Rf 0.47 (hexane : ethyl acetate = 1:1)

Reference example 7



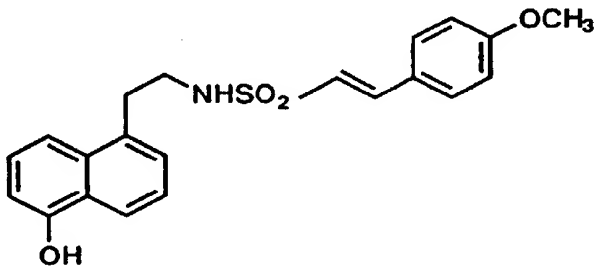
A solution of the compound prepared in reference example 6 (243mg) in methanol (3 ml), pyridinium p-toluenesulfonic acid (PPTS; 30mg) was added. The mixture was stirred overnight at room temperature. Methanol was distilled off, the residue was diluted with ethyl acetate. The organic layer was washed with water and a saturated aqueous solution of sodium chloride, and dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3:2) to give the title compound (204mg) having the following physical data. TLC: Rf 0.16 (hexane : ethyl acetate = 2:1)

Reference example 8



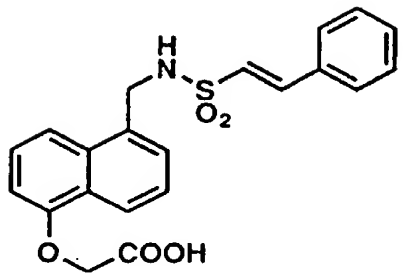
A solution of the compound prepared in reference example 7 (194mg) in methylene chloride (2 ml), trifluoroacetic acid (TFA ; 1mg) and triethylsilane (0.20ml) was added. The mixture was stirred overnight at room temperature. The reaction mixture was neutralized by adding a saturated aqueous solution of sodium bicarbonate, the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, and dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 2:1) to give the title compound (162mg) having the following physical data.
TLC: Rf 0.29 (hexane : ethyl acetate = 1:1)

Reference example 9



To a solution of the compound, 5-[2-[2-hydroxy-2-(4-methoxyphenyl) ethylsulfonylamino]ethyl]-1-tetrahydropyranyloxynaphthalene, prepared by the same procedure as a serise of reaction of reference example 5 and 6 (318mg) using a corresponding compound in methylene chloride (3 ml), triethylamine (0.20ml) and mesyl chloride (83μl) was added at 0°C. The mixture was stirred for 2 hours at room temperature. To the reaction mixture, a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. The residue was dissolved into methanol, and 2N aqueous solution of hydrochloric acid was added to the above mixture. The mixture was stirred for 12 hours at room temperature. The reaction mixture was concentrated. Water was added to the residue, the mixture was extracted with ethyl acetate. The organic layer was washed a saturated aqueous solution of sodium bicarbonate, and dried over magnesium sulfate and concentrated. The reside was purified by column chromatography on silica gel (hexane : ethyl acetate = 2:1) to give the title compound (65mg) having the following physical data.
TLC: Rf 0.54 (hexane : ethyl acetate = 1:1)

Example 3



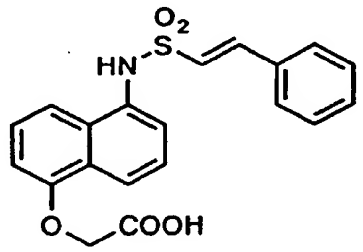
To a solution of the compound prepared in example 1 (84mg) in dimethoxyethane-methanol (2:1, 3ml), 1N aqueous solution of sodium hydroxide (0.5ml) was added. The mixture was stirred for 1 hour at room temperature. To the reaction mixture, 1N hydrochloric acid was added and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, and dried over magnesium sulfate and concentrated. The residue was recrystallized from ethyl acetate-hexane to give the title compound (82mg) having the following physical data.

appearance: white powder
mp: 201-204°C
NMR (DMSO-d6): δ 8.18 (1H, d), 7.88(H, t), 7.73 (1H, d), 7.68-7.30 (9H, m), 7.19 (1H, d), 6.92 (1H, d), 4.86 (2H, s), 4.52 (2H, d).

Example 3(a)-3(ee)

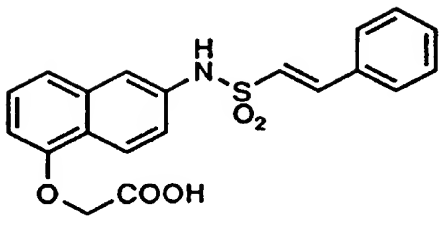
The compounds having the following physical data were obtained by the same procedure as a series of reactions of Reference example 1 → Reference example 2 → Example 1 → Example 3 or Reference example 1 → Example 1 → Example 3.

Example 3(a)



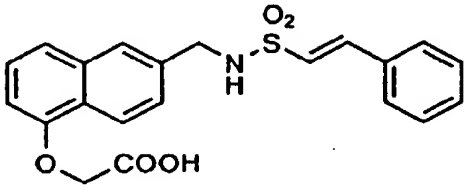
appearance: milk-white powder
mp: 218.5-219.5°C
NMR (DMSO-d6): δ 13.03(1H,brs), 9.95(1H,s), 8.13(1H,dd), 7.84(1H,d), 7.70-7.20(10H,m), 6.87(1H,d), 4.85(2H, s).

Example 3(b)



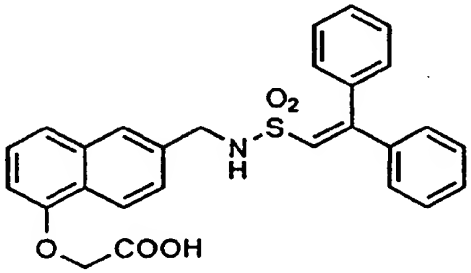
appearance: white powder
mp: 180-181°C
NMR (DMSO-d6): δ 13.05(1H,brs), 10.34(1H,s), 8.12(1H,d), 7.76-7.25(11H,m), 6.76(1H,d), 4.83(2H,s).

Example 3(c)



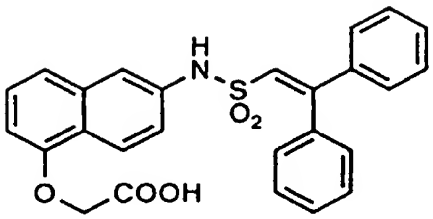
appearance: white powder
mp: 177-179°C
NMR (DMSO-d6): δ 13.08(1H,brs), 8.18(1H,d), 7.97(1H,t), 7.80(1H,s), 7.67-7.28(9H,m), 7.13(1H,d), 6.84(1H,d), 4.84(2H,s), 4.28(2H,d).

Example 3(d)



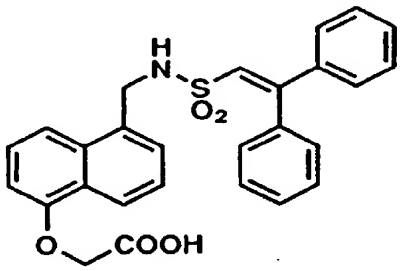
appearance: white powder
mp: 211.8-212.9°C
NMR (DMSO-d6): δ 8.22(1H,d), 7.87(1H,t), 7.81(1H,s), 7.60-7.10(11H,m), 7.00-6.80(3H,m), 6.69(1H,s), 4.87(2H, s), 4.28(2H,d).

Example 3(e)



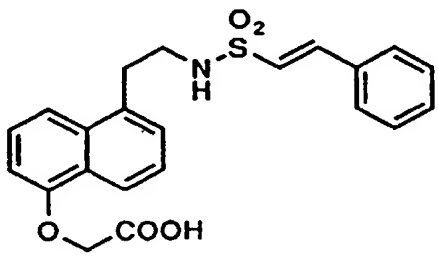
appearance: white powder
TLC : Rf 0.24 (methanol : methylene chloride = 1 : 5)
NMR (DMSO-d6): δ 10.12(1H,s), 8.13(1H,d), 7.50(1H,s), 7.48-7.20(9H,m), 7.10(2H,d), 7.02(2H,d), 6.97(1H,s), 6.77(1H,m), 4.84(2H,s).

Example 3(f)



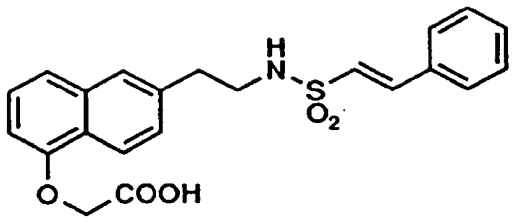
appearance: white powder
mp: 142-143°C
NMR (DMSO-d6): δ 8.22(1H,d), 7.77(1H,t), 7.72(1H,d), 7.59-7.10(12H,m), 7.02(1H,d), 6.94(1H,d), 6.76(1H,s), 4.88(2H,s), 4.54(2H,d).

Example 3(g)



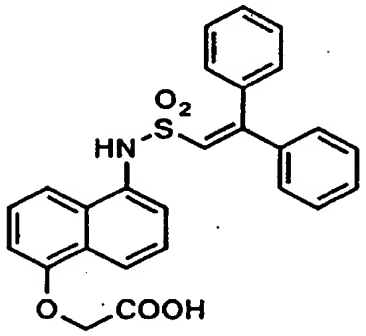
appearance: white powder
mp: 182-184°C
NMR ($CDCl_3$+CD_3OD): δ 8.26(1H,m), 7.64(1H,d), 7.47-7.27(9H,m), 6.74(1H,d), 6.63(1H,d), 4.77(2H,s), 3.34-3.18 (4H,m).

Example 3(h)



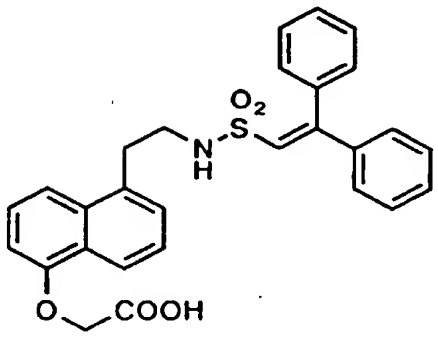
appearance: white powder
mp: 139-141°C
NMR ($CDCl_3$+H_2O): δ 8.25(1H,d), 7.62(1H,s), 7.42-7.24(9H,m), 6.64(1H,d), 6.61(1H,d), 4.80(2H,s), 3.38(2H,t), 3.01(2H,t).

Example 3(i)



appearance: pale yellow powder
mp: 200-202°C
NMR (DMSO-d6): δ 13.08(1H,brs), 9.93(1H,s), 8.19(1H,dd), 7.86(1H,d), 7.56-7.14(15H,m), 7.12-7.00(2H,m), 6.97-6.75(4H,m), 4.89(2H,s).

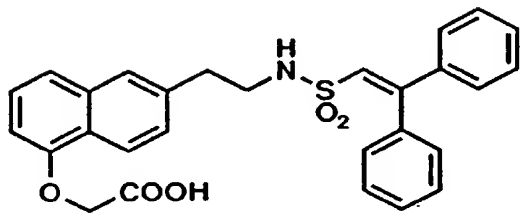
Example 3(j)



appearance: white powder

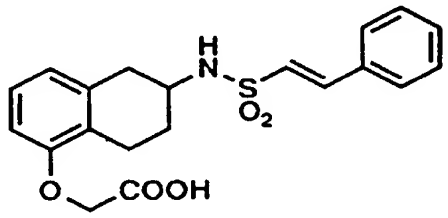
mp: 158-161°C
NMR (DMSO-d6+$CDCl_3$): δ 8.17(1H,m), 7.61(1H,d), 7.46-7.08(13H,m), 6.84(1H,d), 6.76(1H,s), 4.89(2H,s), 3.22 (4H,s like).

Example 3(k)



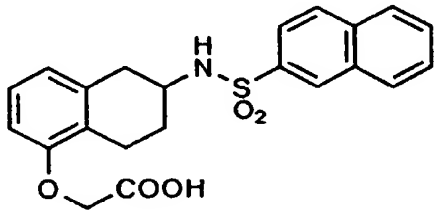
appearance: pale yellow powder
mp: 149-151°C
NMR (DMSO-d6+$CDCl_3$): δ 8.17(1H,d), 7.66(1H,s), 7.50-7.08(13H,m), 6.84-6.73(2H,m), 4.82(2H,s), 3.26(2H,m), 2.92(2H,t).

Example 3(l)



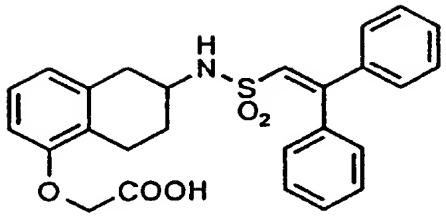
appearance: white powder
mp: 180.5-181.5°C
NMR ($CDCl_3$+CD_3OD): δ 7.60-7.33(6H,m), 7.05(1H,t), 6.82(1H,d), 6.69(1H,d), 6.57(1H,d), 4.61(2H,s), 3.75-3.60 (1H,m), 3.15-2.60(4H,m), 2.20-2.00(1H,m), 1.95-1.70(1H,m).

Example 3(m)



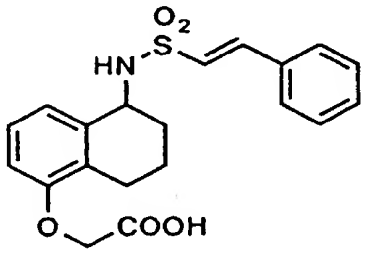
appearance: white powder
mp: 164.6-166.0°C
NMR ($CDCl_3$+CD_3OD): δ 8.45(1H,s), 8.03-7.80(4H,m), 7.72-7.55(2H,m), 7.00(1H,t), 6.56(1H,d), 6.53(1H,d), 4.58 (2H,s), 3.75-3.53(1H,m), 3.00-2.76(2H,m), 2.75-2.50(2H,m), 2.00-1.80(1H,m), 1.80-1.55(1H,m).

Example 3(n)



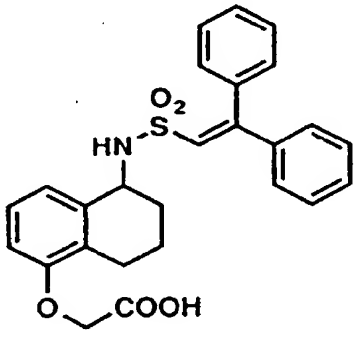
appearance: colourless amorphous
NMR : δ 7.50-7.20(10H,m), 7.05(1H,t), 6.87(1H,s), 6.65(1H,d), 6.55(1H,d), 4.65(2H,s), 4.20-3.20(1H,br), 4.03(1H, d), 3.59(1H,m), 3.02-2.40(4H,m), 2.13-1.74(1H,m), 1.74-1.50(1H,m).

Example 3(o)



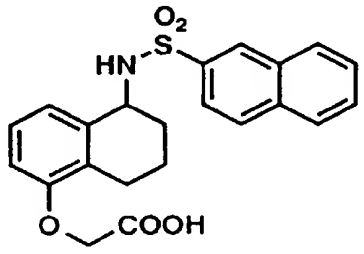
appearance: white powder
mp: 210.7-211.5°C
NMR ($CDCl_3$+CD_3OD): δ 7.60-7.40(6H,m), 7.17-7.00(2H,m), 6.90(1H,d), 6.62(1H,dd), 4.62(2H,s), 4.50(1H,t), 2.90-2.55(2H,m), 2.10-1.70(4H,m) .

Example 3(p)



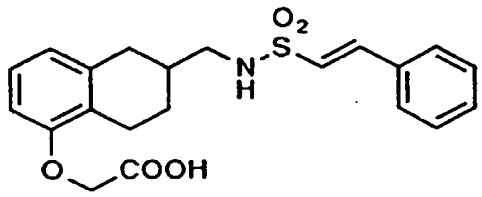
appearance: white powder
mp: 184.5-185.3°C
NMR ($CDCl_3$+CD_3OD): δ 7.53-7.20(10H,m), 7.20-7.00(2H,m), 6.90(1H,s), 6.62(1H,d), 4.62(3H,m), 2.88-2.48(2H, m), 2.10-1.50(4H,m).

Example 3(q)



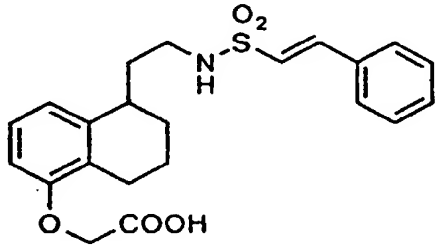
appearance: white powder
mp: 230.8-231.2°C
NMR ($CDCl_3$+CD_3OD): δ 8.50(1H,s), 8.05-7.85(4H,m), 7.74-7.58(2H,m), 6.95(1H,t), 6.61(1H,d), 6.56(1H,d), 4.57 (2H,s), 4.47(1H,m), 2.88-2.67(1H,m), 2.67-2.40(1H,m), 2.00-1.60(4H,m).

Example 3(r)



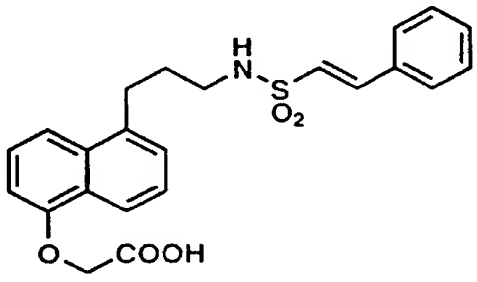
appearance: white powder
mp: 159-160°C
NMR : δ 7.45(6H,m), 7.05(1H,t), 6.75(1H,d), 6.73(1H,d), 6.55(1H,d), 4.67(1H,s).

Example 3(s)



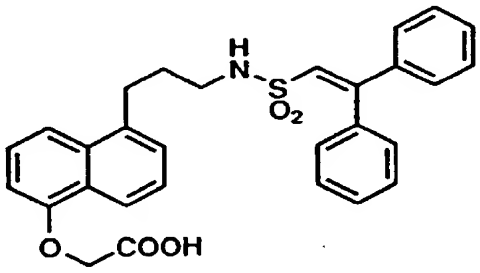
appearance: white powder
NMR : δ 7.55-7.32(8H,m), 6.99(1H,d), 6.81-6.68(2H,m), 6.52(1H,d), 500(1H,brs) ,4.63(2H,s), 3.15(2H,m), 2.95-2.51(4H,m), 2.06-1.53(6H,m).
mp: 101.0-103.0°C.

Example 3(t)



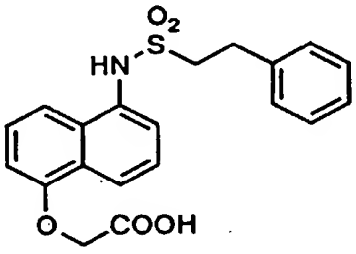
TLC : 0.30 (methanol : methylene chloride = 1:5)
NMR ($CDCl_3$+CD_3OD): δ 8.12 (1H, dd), 7.47 (1H, d), 7.40-7.10 (9H, m), 6.63 (1H, d), 6.60 (1H, d), 4.65 (2H, s), 2.97 (4H, m), 1.87 (2H, m).

Example 3(u)



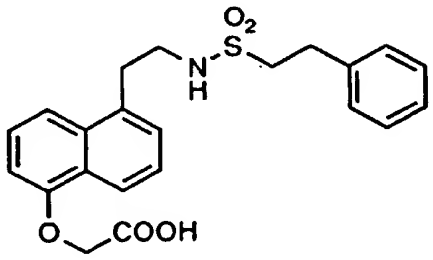
TLC : Rf 0.30 (methanol : methylene chloride = 1 : 4)
NMR ($CDCl_3$+CD_3OD): δ 8.25 (1H, d), 7.60-7.15 (14H, m), 6.78 (1H, s), 6.75 (1H, d), 4.78 (2H, s), 3.05-2.82 (4H, m), 1.73 (2H, m).

Example 3(v)



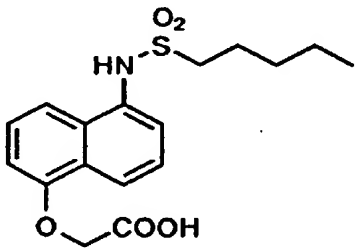
TLC : Rf 0.26 (30% methanol / chloroform)
NMR (CD_3OD:$CDCl_3$=2:1): δ 8.33 (1 H, d), 7.88 (1 H, d), 7.64 (1 H, d), 7.54-7.42 (2 H, m), 7.30-7.03 (5 H, m), 6.87 (1 H, d), 4.83 (2 H, s), 3.40-3.27 (2 H, m), 3.18-3.05 (2 H, m).

Example 3(w)



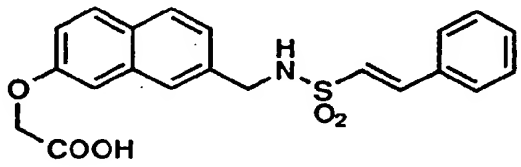
TLC : Rf 0.29 (30% methanol / chloroform)
NMR ($CDCl_3$: CD_3OD = 1:2) : δ 8.31 (1H, m), 7.71 (1 H, d), 7.52-7.06 (8 H, m), 6.81 (1 H, d), 4.80 (2 H, s), 3.48-3.22 (4 H, m), 3.17-2.89 (4 H, m).

Example 3(x)



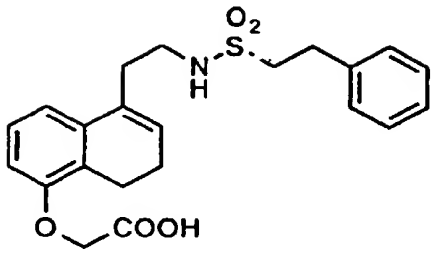
TLC : Rf 0.26 (30% methanol / chloroform)
NMR (CD_3OD:$CDCl_3$=2:1): δ 8.33 (1 H, d), 7.84 (1 H, d), 7.62 (1 H, d), 7.53-7.40 (2 H, m), 6.87 (1 H, d), 4.84 (2 H, s), 3.14-3.02 (2 H, m), 1.93-1.74 (2 H, m), 1.42-1.16(4H, m), 0.85 (3 H, t).

Example 3(y)



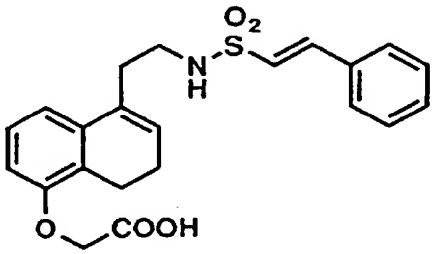
TLC : Rf 0.19 (25%methanol / chloroform)
NMR (DMSO-d6): δ 13.02 (1 H, br s), 7.93 (1 H, t), 7.83-7.68 (3 H, m), 7.63-7.51 (2 H, m), 7.43-7.04 (8 H, m), 4.77 (2 H, s), 4.26 (2 H, d).

Example 3(z)



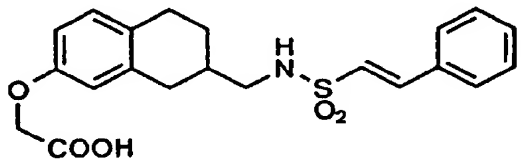
TLC : Rf 0.32 (30%methanol / chloroform)
NMR : δ 7.33-7.07 (6 H, m), 6.88 (1 H, d,), 6.68 (1 H, d), 5.94 (1 H, 7), 500-4.00 (1 H, br s), 4.65 (2 H, s), 4.32 (1 H, t), 3.28-2.95 (4 H, m), 2.80 (2 H, t), 2.65 (2 H, t), 2.22 (2 H, m).

Example 3(aa)



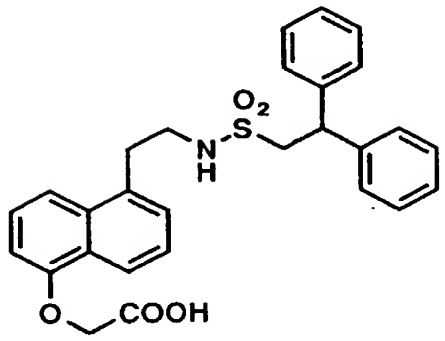
TLC : Rf 0.29 (30%methanol / chloroform)
NMR ($CDCl_3$: CD_3OD= 1:2): δ 7.54-7.30 (6 H, m), 7.04 (1 H, t), 6.91 (1 H, d), 6.80 (1 H, d), 6.67 (1 H, d), 5.95 (1 H, t), 4.60 (2 H, s), 3.15 (2 H, t), 2.84-2.63 (4 H, m), 2.19 (2 H, m).

Example 3(bb)



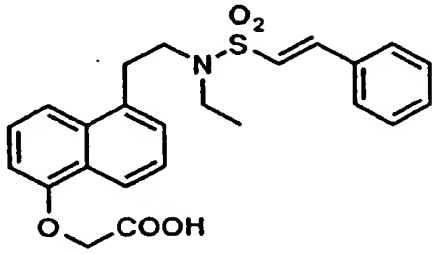
TLC : Rf 0.24 (30%methanol / chloroform)
NMR (DMSO-d6): δ 12.90(1 H, brs), 7.87-7.64 (2 H, m), 7.49-7.26 (5 H, m), 7.19 (1 H, d), 6.94 (1 H, d), 6.67-6.55 (2 H, m), 4.55 (2 H, s), 2.95-2.27 (6 H, m), 2.00-1.74 (2 H, m), 1.44-1.20 (1 H, m).

Example 3(cc)



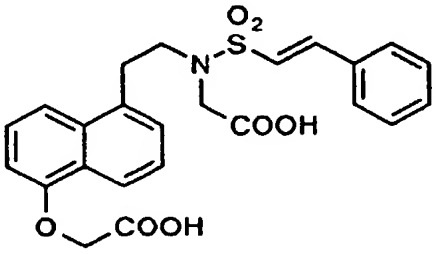
TLC: Rf 0.29 (chloroform: methanol = 5 : 1)
NMR ($CDCl_3$ + CD_3OD): δ 8.094 (1 H, d), 7.28-7.03 (14H, m), 6.58 (1 H, d), 4.50 (1H, t), 4.45 (2H, s), 3.64 (2H, d), 2.89-2.85 (2H, m), 2.79-2.75 (2 H, m).

Example 3(dd)



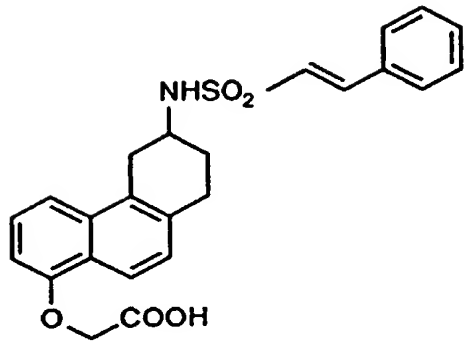
TLC: Rf 0.50 (chloroform: : 0.1) methanol : acetic acid = 19
NMR (DMSO-d6): δ 8.16 (1H, dd), 7.75-7.66 (3H, m), 7.50-7.35 (7H, m), 7.25 (1H, d), 6.89 (1H, d), 4.87 (2H, s), 3.60-3.30 (4H, m), 3.28 (2H, q), 1.14 (3H, t).

Example 3(ee)



TLC : Rf 0.08 (chloroform : methanol = 5 : 1)
NMR (CD_3OD): δ 8.28-8.22 (1H, m), 7.22 (1H, d), 7.50-7.32 (9H, m), 6.84 (1H, d), 6.79 (1H, d), 4.80 (2H, s), 4.07 (2H, s), 3.60-3.51 (2H, m), 3.44-3.35 (2H, m).

Example 3(ff)



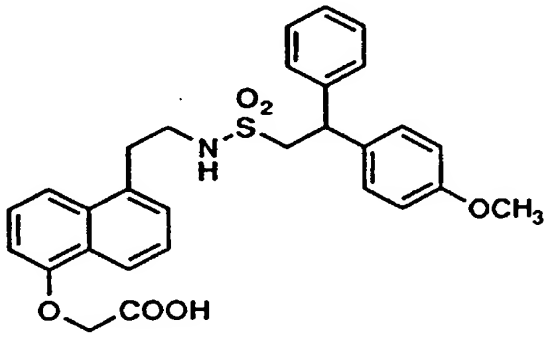
The title compound having the following physical data was obtained by the same procedure of Example 3, using the compound prepared in Example 2.

TLC : Rf 0.21 (30%methanol / chloroform)
NMR (DMSO-d6): δ 12.96(1 H, brs), 8.04 (1 H, d), 7.75-7.55 (3 H, m), 7.50-7.15 (8 H, m), 6.81 (1 H, d), 4.81 (2 H, s),3.78-3.30 (2 H, m), 3.07-2.81 (3 H, m), 2.21-2.03 (1 H, m), 1.94-1.68 (1 H, m).

Example 3(gg)-3(ll)

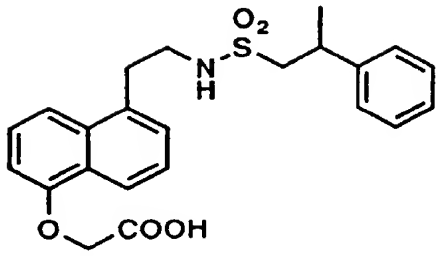
The compounds having the following physical data were obtained by the same procedure as a series of reactions of Example 2 → Example 3, using the compound prepared in Reference example 8 or Reference example 9, or by the same procedure as a series of reactions of Reference example 5 → Reference example 6 → Reference example 7 → Reference example 8 → Example 2 → Example 3 or Reference example 5 → Reference example 6 → Reference example 9 → Example 2 → Example 3 using corresponding compounds.

Example 3(gg)



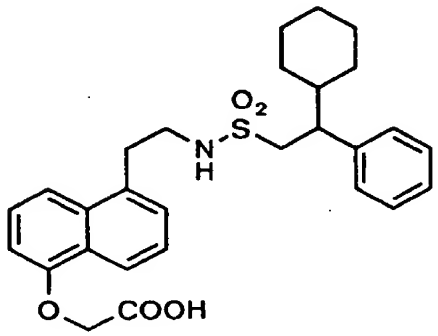
TLC : Rf 0.30 (25% methanol / chloroform)
NMR (DMSO-d6): δ 8.17 (1H, d), 7.59-7.05 (11H, m), 6.91-6.72 (3H, m), 4.72 (2H, s), 4.37 (1H, t), 4.20-3.20 (7H, m), 3.15-3.00 (4H, m).

Example 3(hh)



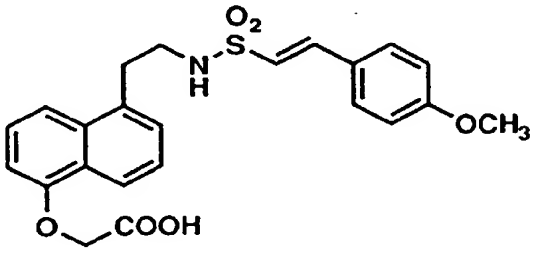
TLC : Rf 0.26 (25% methanol / chloroform)
NMR (DMSO-d6): δ 8.16 (1H, m), 7.70-7.11 (9H, m), 6.89 (1H, d), 4.86 (2H, s), 3.80-2.90 (9H, m), 1.50 (3H, d).

Example 3(ii)



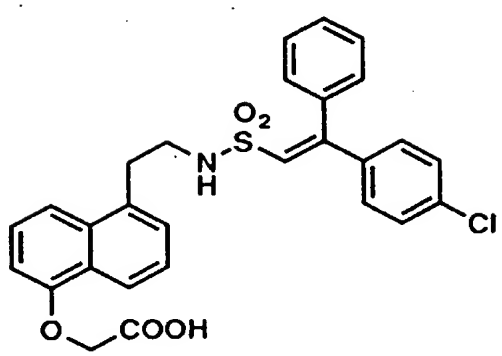
TLC : Rf 0.32 (25% methanol / chloroform)
NMR (DMSO-d6): δ 8.18 (1H, d), 7.60-6.80 (11H, m), 4.88 (2H, s), 3.60-2.80 (8H, m), 2.00-0.50 (11H, m).

Example 3(jj)



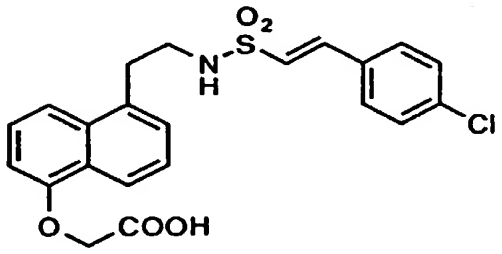
TLC : Rf 0.38 (chloroform: : 1 : methanol : acetic acid = 19 0.1)
NMR (DMSO-d6): δ 8.20-8.10 (1H, m), 7.68-7.57 (3H, m), 7.48-7.25 (5H, m), 7.00-6.83 (4H, m), 4.85 (2H, s), 3.79 (3H, s), 3.50-3.10 (4H, m).

Example 3(kk)



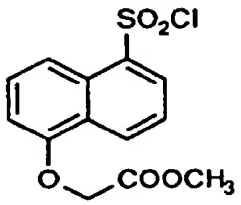
TLC : Rf 0.49 (chloroform : methanol : acetic acid = 19 : 1 : 0.1)
NMR (DMSO-d6): δ 8.20-8.10 (1H, m), 7.62-7.52 (1H, m), 7.50-7.08 (13H, m), 6.90-6.78 (2H, m), 4.70 (2H, s), 3.30-3.10 (4H, m).

Example 3(ll)



TLC: Rf 0.25 (chloroform : methanol = 3 : 1)
NMR : δ 8.33-8.26 (1H, m), 7.57 (1H, d), 7.45-7.20 (8H, m), 6.99 (1H, d), 6.37 (1H, d), 4.77 (2H, s), 4.60-4.50 (1H, br), 3.52-3.28 (4H, m).

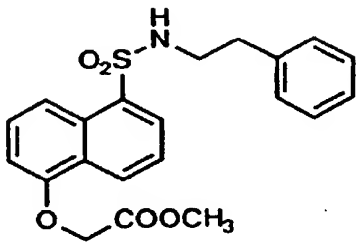
Reference example 10



To a solution of sodium 5-hydroxynaphthalenesulphonate (10g) in dimethylformamide (50ml), sodium carbonate (6.46g) and methyl bromoacetate (9.32g) were added. The mixture was stirred for 10 hours at 100°C. The reaction mixture was filtered and the filtrate was concentrated. To a solution of the residue in dimethylformamide (50ml), thionylchloride (9.67g) was added at 0°C. The mixture was stirred for 30 minutes at 0°C. To the reaction mixture, water was added and filtered. The residue was washed with hexane and dried over to give the title compound having the following physical data.

TLC: Rf 0.17 (ethyl acetate : hexane = 1:5)
NMR : δ 8.83 (1H, d), 8.46-8.35 (2H, m), 7.68 (1H, t), 7.62 (1H, t), 6.92 (1H, d), 4.87 (2H, s), 3.84 (3H, s).

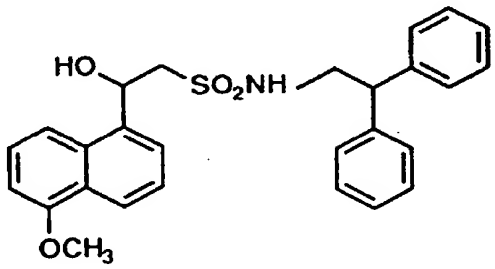
Example 4



To the compound prepared in reference example 10 (0.315g) in methylene chloride (5 ml), a solution of 2-phenylethylamine (0.158g) in methylene chloride (10 ml) and triethylamine (0.395g) was dropped. The mixture was stirred for 4 hours at room temperature. Water was poured into the reaction mixture. The mixture was extracted with ethyl acetate. The organic layer was washed 1N hydrochloric acid and water, and dried over sodium sulfate and concentrated. The residue was recrystallized from ethyl acetate-hexane to give the title compound (0.279mg) having the following physical data.

appearance: pale yellow powder
mp: 97.5-98.5°C
NMR : δ 8.67 (1H, d), 8.27 (1H, d), 8.12 (1H, d), 7.56 (1H, t), 7.47 (1H, t), 7.20-7.10 (3H, m), 6.96-6.87 (2H, m), 6.81 (1H, d), 4.87 (2H, s), 4.55 (1H, t), 3.84 (3H, s), 3.17 (2H, dt), 2.65 (2H, t).

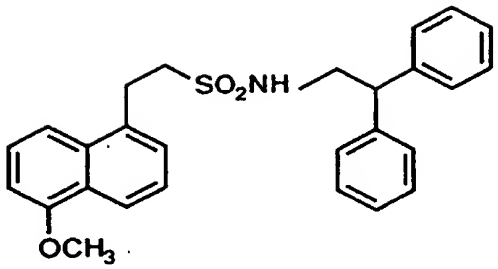
Reference example 11



To a solution of N-(2,2-diphenylethyl)methanesulfoneamide (5.51 g) in THF (60 ml) and TMEDA (12.1 ml), n-butyl lithium(1.66M in hexane; 24.1ml) was dropped at -78 °C. The mixture was stirred to warm up to -20°C for 2.5 hours, and was recooled to -70 °C. A solution of the 5-aldehyde-1-methoxynaphthalene (3.72 g) in THF (20 ml) was slowly added to the above solution at -50 °C. The mixture was stirred to warm up to -15 °C. To the reaction mixture, 1N aqueous solution of hydrochloric acid was added, and then the mixture was extracted with ethyl acetate. The organic layer was washed with water, a saturated aqueous solution of sodium chloride, dried over magnesium sulfate and concentrated to give the title compound (6.64g) having following physical data.

TLC : Rf 0.37 (ethyl acetate : hexane = 1 : 2);
NMR : δ 8.29 (1 H, d,), 7.70 (1 H, d), 7.54-7.38 (3 H, m), 7.38-7.13 (10 H, m), 6.84 (1 H, d), 5.95 (1 H, m), 4.45 (1 H, t), 4.19 (1 H, t), 4.00 (3 H, s), 3.74 (2 H, t), 3.42-3.23 (2 H, m).

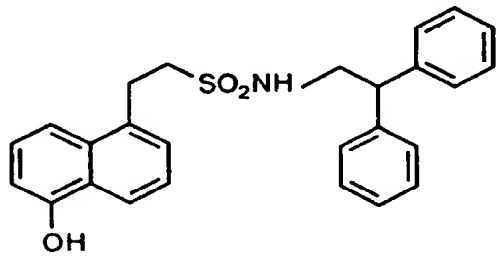
Reference example 12



To a solution of the compound prepared in reference example 11 (130 g) in methylene chloride (870 ml) and TFA (271 ml), triethylsilane (81.9 g) was added at room temperature. The mixture was stirred for 15 hours at room temperature. The reaction mixture was concentrated. The residue was dissolved with ethyl acetate and the solution was filtered to remove the white precipitate. The filtrate was concentrated. The residue was purified by the column chromatography (ethyl acetate : hexane = 1 : 6 → 1 : 3) to give the title compound (95.1 g) having following physical data.

TLC : Rf 0.43 (ethyl acetate : hexane = 1 : 2);
NMR : δ 8.23 (1 H, d), 7.55-7.10 (15 H, m), 6.85 (1 H, d), 4.08-3.93 (4 H, m), 3.58 (2 H, dd), 3.53-3.37 (2 H, m), 3.37-3.22 (2 H, m).

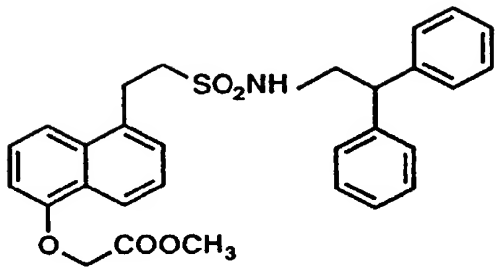
Reference example 13



To a solution of the compound prepared in reference example 12 (94.0 g) in methylene chloride (700 ml), boron tribromide (158.6 g) in methylene chloride (300 ml) was added at - 30 °C. The mixture was stirred to warm up to 0 °C for 2 hours. The reaction mixture was poured into ice water. The suspension was filtered to collect the white precipitate, which was washed with water, ether, dried over to give the title compound (76.9 g). The combined filtrate was extracted with methylene chloride. The organic layer was washed with water, dried over sodium sulfate and concentrated to give the title compound (9.0 g; total 85.9 g) having following physical data.

TLC : Rf 0.26 (ethyl acetate : hexane = 1 : 2);
NMR : δ 8.20 (1 H, d), 7.50-7.10 (14 H, m), 6.87 (1 H, d), 4.05 (1 H, t), 3.59 (2 H, d), 3.50-3.37 (2 H, m), 3.37-3.20 (2 H, m).

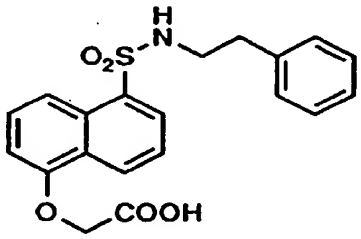
Example 5



To a solution of the compound prepared in reference example 13 (2.99 g) in DMF (70 ml), sodium bicarbonate (1.10 g) and methyl bromoacetate (1.59 g) was added at room temperature. The mixture was stirred overnight at 100 °C. The reaction mixture was filtered to remove the white precipitate and the filtrate was concentrated. The residue was purified by the column chromatography (ethyl acetate : benzene = 1 : 10) to give the title compound (2.33 g) having following physical data.

TLC : Rf 0.23 (ethyl acetate : hexane = 1 : 2);
NMR : δ 8.32 (1 H, d), 7.57 (1 H, d), 7.50-7.07 (13 H, m), 6.74 (1 H, d), 4.83 (2 H, s), 4.15-3.93 (2 H, m), 3.82 (3 H, s), 3.61 (2 H, t), 3.53-3.35 (2 H, m), 3.35-3.20 (2 H, m).

Example 6



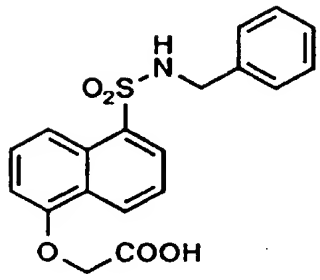
To a solution of the compound prepared in example 4 (0.256g) in methanol-dimethoxyethane (2ml-5ml), 2N aqueous solution of sodium hydroxide (1.5ml) was added. The mixture was stirred for 3 hours at room temperature. 2N hydrochloric acid was neutralized by adding to the reaction mixture. White precipitate was collected by filtration, and washed with water and ether, and dried over to give the title compound (0.125mg) having the following physical data.

appearance: white powder
mp: 174.4-176.2°C
NMR ($CDCl_3$+CD_3OD): δ 8.68(1H, d), 8.23(1H, d), 8.13(1H, d), 7.53(1H, t), 7.50(1H, t), 7.23-7.07(3H, m), 7.00-6.80 (3H, m), 4.83(2H, s), 3.13(2H, t), 2.63(2H, t).

Example 6(a)-6(d)

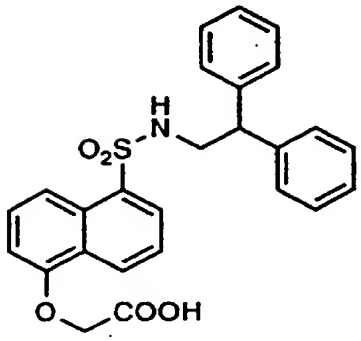
The compounds having the following physical data were obtained by the same procedure as a series of reactions of Reference example 10 → Example 4 → Example 6.

Example 6(a)



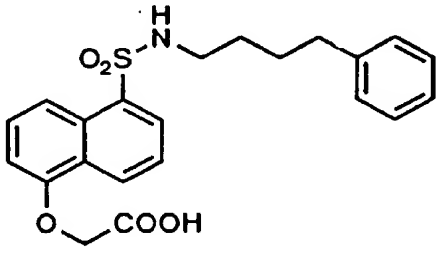
appearance: white powder
mp: 200.2-201.7°C
NMR ($CDCl_3$+CD_3OD): δ 8.67(1 H, d), 8.25(2H, d), 7.54(1H, t), 7.50(1H, t), 7.20-7.00(5H, m), 6.89(1H, d), 4.83 (2H, s), 4.03(2H, s).

Example 6(b)



appearance: white powder
mp: 198.7-199.0°C
NMR ($CDCl_3$+CD_3OD): δ 8.73(1H, d), 8.28(1H, d), 8.00(1H, d), 7.57(1H, t), 7.42(1H, t), 7.25-7.07(6H, m), 7.00-6.83 (5H, m), 4.87(2H, s), 4.00-3.68(1H, m), 3.48(2H, d).

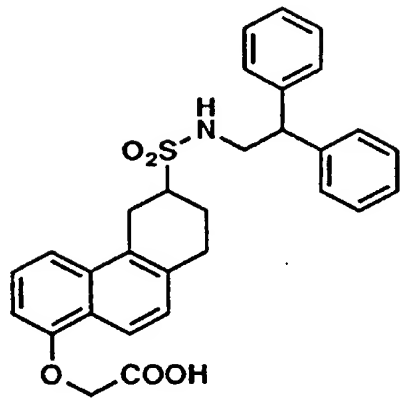
Example 6(c)



appearance: white powder
mp: 162.1-164.5°C
NMR ($CDCl_3$+CD_3OD): δ 8.67 (1H, d), 8.23 (2H, d), 7.53 (2H, t), 7.28-7.07 (3H, m), 7.00 (2H, d), 6.88 (1H, d), 4.83

(2H, s), 2.87 (2H, t), 2.43 (2H, t), 1.60-1.27(4H, m).

Example 6(d)

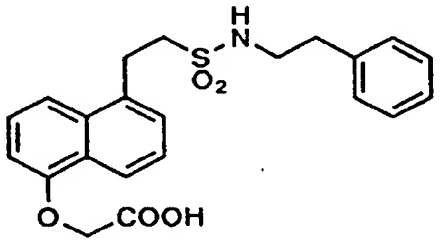


TLC : Rf 0.25 (30% methanol / chloroform)
NMR (DMSO-d6) : δ 13.02 (1H, brs), 8.00 (1H, d), 7.78-7.18 (13H, m), 6.93 (1H, d), 4.85 (2H, s), 4.22 (1H, t), 4.02-3.80 (1H, m), 3.60-2.80 (7H, m), 2.30-1.80 (2H, m).

Example 6(e)-6(f)

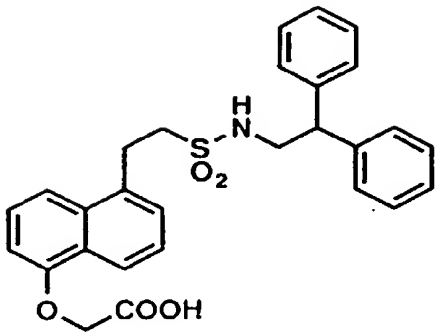
The compounds having the following physical data were obtained by the same procedure as Example 6, using the compound prepared in Example 5, or by the same procedure as a series of reactions of Reference example 11 → Reference example 12 → Reference example 13 → Example 5 → Example 6, using a corresponding compound.

Example 6(e)



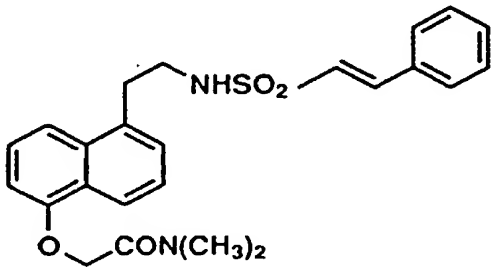
TLC : Rf 0.15 (methanol : methylene chloride = 1 : 5)
NMR ($CDCl_3$+CD_3OD): δ 8.32 (1H, d), 7.57 (1H, d), 7.47-7.10 (8H, m), 6.78 (1H, d), 4.80 (2H, s), 3.53-3.35 (2H, m), 3.35-3.20 (4H, m), 2.78 (2H, t).

Example 6(f)



TLC : Rf 0.21 (methanol : methylene chloride = 1 : 5)
NMR (DMSO-d6): δ 8.17 (1H, d), 7.57-7.10 (14H, m), 6.91(1H, d), 4.89 (2H, s), 4.18 (1H, t), 3.67 (2H, m), 3.60-3.00 (4H, m).

Example 7



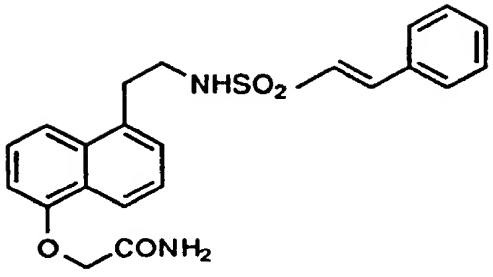
A solution of the compound (0.061g), example 2(g), prepared in reference example 1, 2 and example 1 using a corresponding compound in THF(0.5ml), 50% aqueous solution of dimethylamine (0.1 ml)was added. The mixture was stirred for 4 hours at room temperature. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with 1N aqueous solution of hydrochloric acid and a saturated aqueous solution of sodium chloride, and dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (chloroform : methanol = 19 : 1), and crystallized from chloroform-diethyl ether to give the title compound (0.051g) having the following physical data.

TLC: Rf 0.60 (chloroform : methanol = 9 : 1)
NMR: δ 8.24 (1H, dd), 7.58 (1H, d), 7.45-7.26 (9H, m), 6.84 (1H, d), 6.54 (1H, d), 4.85 (2H, s), 4.47 (1H, t), 3.43 (2H, t), 3.32 (2H, t), 3.13 (3H, s), 3.00 (3H, s).

Example 7 (a)-(b)

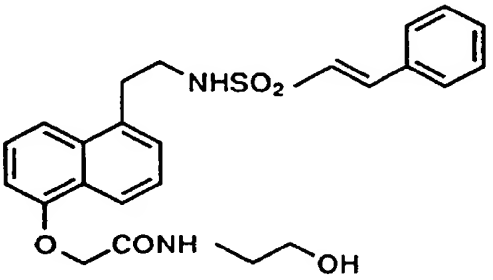
The compounds having the following physical data were obtained by the same procedure as Example 7.

Example 7 (a)



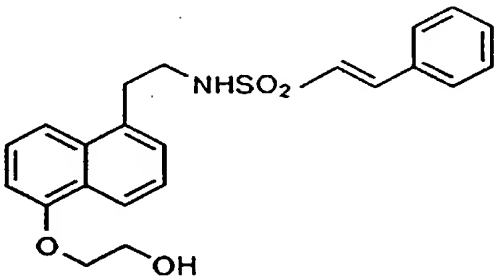
TLC: Rf 0.59 (chloroform : methanol = 9 : 1)
NMR: δ 8.14 (1H, dd), 7.66 (1H, d), 7.48-7.32 (9H, m), 6.78 (1H, d), 6.55 (1H, d), 4.63 (2H, s), 3.42-3.30 (4H, m).

Example 7 (b)



TLC: Rf 0.50 (chloroform : methanol = 9 : 1)
NMR ($CDCl_3$+CD_3OD) : δ 8.16 (1H, dd), 7.65 (1H, d), 7.48-7.28 (9H, m), 6.76 (1H, d), 6.55 (1H, d), 5.40 (1H, t), 4.64 (2H, s), 3.73 (2H, t), 3.53 (2H, t), 3.44-3.29 (4H, m).

Example 8



A solution of a compound (0.118g), example 2(g), piepared in reference example 1, 2 and example 1 using a corresponding compound in methanol-THF(2ml-1 ml), sodium borohydride (0.057g) was added. The mixture was stirred for 5 hours at room temperature. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with 1N aqueous solution of hydrochloric acid and a saturated aqueous solution of sodium chloride, and dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 2 : 1) to give the title compound (0.106g) having the following physical data.

TLC: Rf 0.15 (hexane : ethyl acetate = 2 : 1)
NMR (DMSO-d6) : δ 8.204 (1H, dd), 7.72-7.57 (4H, m), 7.49-7.34 (6H, m), 7.16 (1H, d), 6.97 (1H, d), 5.01 (1H, t), 4.17 (2H, t), 3.90 (2H, t), 3.38-3.35 (1H, m), 3.28-3.26 (4H, m).

Compounds prepared in the foregoing Examples are as follows. The Example number precedes the name of each compound:

Example 3	5-[(2-phenylvinyl)sulfonylaminomethyl]naphthyloxyacetic acid,
Example 3(a)	5-[(2-phenylvinyl)sulfonylamino]naphthyloxyacetic acid,
Example 3(b)	6-[(2-phenylvinyl)sulfonylamino]naphthyloxyacetic acid,
Example 3(c)	6-[(2-phenylvinyl)sulfonylaminomethyl]naphthyloxyacetic acid,
Example 3(d)	6-[(2,2-diphenylvinyl)sulfonylaminomethyl]-naphthyloxyacetic acid,
Example 3(e)	6-[(2,2-diphenylvinyl)sulfonylamino]naphthyloxyacetic acid,
Example 3(f)	5-[(2,2-diphenylvinyl)sulfonylaminomethyl]-naphthyloxyacetic acid,
Example 3(g)	5-[2-[(2-phenylvinyl)sulfonylamino]ethyl]-naphthyloxyacetic acid,
Example 3(h)	6-[2-[(2-phenylvinyl)sulfonylamino]ethyl]-naphthyloxyacetic acid,
Example 3(i)	5-[(2,2-diphenylvinyl)sulfonylamino]-naphthyloxyacetic acid,
Example 3(j)	5-[2-[(2,2-diphenylvinyl)sulfonylamino]ethyl]-naphthyloxyacetic acid,
Example 3(k)	6-[2-[(2,2-diphenylvinyl)sulfonylamino]ethyl]-naphthyloxyacetic acid,
Example 3(l)	6-[(2-phenylvinyl)sulfonylamino]-5,6,7,8-tetrahydronaphthyloxyacetic acid,
Example 3(m)	6-(naphth-2-yl-sulfonylamino)-5,6,7,8-tetrahydronaphthyloxyacetic acid,
Example 3(n)	6-[(2,2-diphenylvinyl)sulfonylamino]-5,6,7,8-tetrahydronaphthyloxyacetic acid,
Example 3(o)	5-[(2-phenylvinyl)sulfonylamino]-5,6,7,8-tetrahydronaphthyloxyacetic acid,
Example 3(p)	5-[(2,2-diphenylvinyl)sulfonylamino]-5,6,7,8-tetrahydronaphthyloxyacetic acid,
Example 3(q)	5-(naphth-2-yl-sulfonylamino)-5,6,7,8-tetrahydronaphthyloxyacetic acid,
Example 3(r)	6-[(2-phenylvinyl)sulfonylaminomethyl]-5,6,7,8-tetrahydronaphthyloxyacetic acid,
Example 3(s)	5-[2-[(2-phenylvinyl)sulfonylamino]ethyl]-5,6,7,8-tetrahydronaphthyloxyacetic acid,
Example 3(t)	5-[3-[(2-phenylvinyl)sulfonylamino]propyl]-naphthyloxyacetic acid,
Example 3(u)	5-[3-[(2,2-diphenylvinyl)sulfonylamino]propyl)-naphthyloxyacetic acid,
Example 3(v)	5-[(2-phenylethyl)sulfonylamino]naphthyloxyacetic acid,
Example 3(w)	5-[2-[(2-phenylethyl)sulfonylamino]ethyl]-naphthyloxyacetic acid,
Example 3(x)	5-(pentylsulfonylamino)naphthyloxyacetic acid,
Example 3(y)	6-[(2-phenylvinyl)sulfonylaminomethyl]naphth-3-yloxyacetic acid,
Example 3(z)	5-[2-[(2-phenylethyl)sulfonylamino]ethyl]-7,8-dihydronaphthyloxyacetic acid,
Example 3(aa)	5-[2-[(2-phenylvinyl)sulfonylamino]ethyl]-7,8-dihydronaphthyloxyacetic acid,
Example 3(bb)	6-[(2-phenylvinyl)sulfonylaminomethyl]-5,6,7,8-dihydronaphth-3-yloxyacetic acid,
Example 3(cc)	5-[2-[(2,2-diphenylethyl)sulfonylamino]ethyl]-naphthyloxyacetic acid,
Example 3(dd)	5-[2-[(2-phenylvinyl)sulfonyl-N-ethylamino]ethyl]naphthyloxyacetic acid,
Example 3(ee)	5-[2-[(2-phenylvinyl)sufonyl-N-carboxymethylamino]-ethyl]naphthyloxyacetic acid,
Example 3(gg)	5-[2-[[2-(4-methoxyphenyl)-2-phenylethyl]-sulfonylamino]-ethyl]-naphthyl oxyacetic acid,
Example 3(hh)	5-[2-[(2-phenylpropyl)sulfonylamino]ethyl]-naphthyloxyacetic acid,
Example 3(ii)	5-[2-[(2-cyclohexyl-2-phenylethyl)sulfonylamino]-ethyl]naphthyloxyacetic acid,
Example 3(jj)	5-[2-[[2-(4-methoxyphenyl)vinyl]sulfonylamino]-ethyl]naphthyloxyacetic acid,
Example 3(kk)	5-[2-[[2-(4-chlorophenyl)-2-phenylvinyl]-sulfonylamino]-ethyl]naphthyloxyacetic acid,
Example 3(11)	5-[2-[[2-(4-chlorophenyl)vinyl]sulfonylamino]-ethyl]naphthyloxyacetic acid,
Example 7	5-[2-[(2-phenylvinyl)sulfonylamino]ethyl]-1-N,N-dimethylaminocarbonylmethyloxynaphthalene,
Example 7(a)	5-[2-[(2-phenylvinyl)sulfonylamino]ethyl]-naphthyloxyacetamide,
Example 7(b)	5-[2-[(2-phenylvinyl)sulfonylamino)ethyl]-1-(2-hydroxyethyl)aminocarbonylmethyloxynaphthalene,
Example 8	5-[2-[(2-phenylvinyl)sulfonylamino]ethyl]-1-(2-hydroxyethyl)oxynaphthalene,
Example 3(ff)	6-[(2-phenylvinyl)sulfonylamino]-5,6,7,8-tetrahydrophenanthrene-l-yloxyacetic acid,
Example 6	5-[N-(2-phenylethyl)sulfamoyl]naphthyloxyacetic acid,
Example 6(a)	5-(N-phenylmethylsulfamoyl)naphthyloxyacetic acid,
Example 6(b)	5-[N-(2,2-diphenylethyl)sulfamoyl]naphthyloxyacetic acid,
Example 6(c)	5-[N-(4-phenylbutyl)sulfamoyl]naphthyloxyacetic acid,
Example 6(f)	5-[2-[N-(2,2-diphenylethyl)sulfamoyl]ethyl]-naphthyloxyacetic acid,
Example 6(e)	5-[2-[N-(2-phenylethyl)sulfamoyl]ethyl]naphthyloxyacetic acid, and
Example 6(d)	6-[(2,2-diphenylethyl)sulfamoyl]-5,6,7,8-tetrahydrophenanthren-l-yloxyacetic acid.

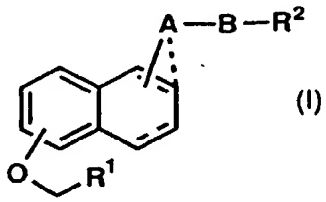
Formulation example 1:

The following compounds were admixed in conventional method and punched out to obtain 100 tablets each containing 5mg of active ingredient.

5-[(2-phenylvinyl)sulfonylaminomehtyl]naphthyloxy acetic acid	500 mg
Carboxymethylcellulose calcium	200 mg
Magnesium stearate	100 mg
Micro crystalline cellulose	9.2 g

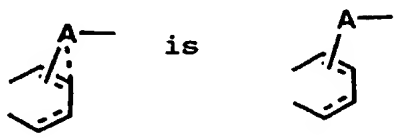
Claims

1. A naphthyloxyacetic acid derivative of the formula (I):

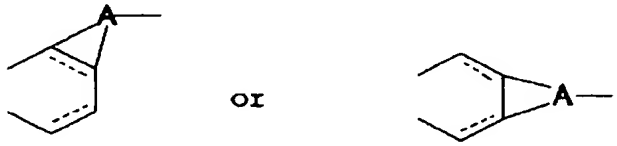


(I)

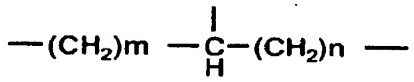
wherein R^1 is (i) $-COOR^4$ in which R^4 is hydrogen or C1-4 alkyl, (ii) $-CONR^5R^6$ in which R^5 and R^6 each, independently, is hydrogen, C1-4 alkyl or C1-4 alkyl substituted by a hydroxy group, or (iii) $-CH_2OH$;



in which A is a bond or C1-4 alkylene, or

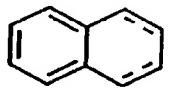


in which A is



in which m is 0, 1, 2, 3 or 4, n is 0, 1, 2, 3 or 4, and m + n is 2, 3 or 4;
B is $-NR^3SO_2-$ or $-SO_2NR^3-$ in which R^3 is hydrogen, C1-4 alkyl or $-CH_2COOR^7$ in which R^7 is hydrogen or a group R^{4a} in which R^{4a} is C1-4 alkyl;
R^2 is (i) C1-6 alkyl, C2-6 alkenyl or C2-6 alkynyl, or

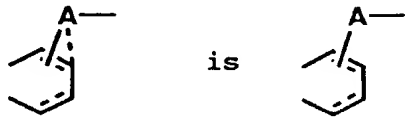
(ii) C1-6 alkyl, C2-6 alkenyl or C2-6 alkynyl substituted by one, two or three substituents selected from phenyl, C4-7 cycloalkyl or phenyl substituted by one, two or three substituents selected from C1-4 alkyl, C1-4 alkoxy or halogen and in the formula



—— is a single bond or double bond;

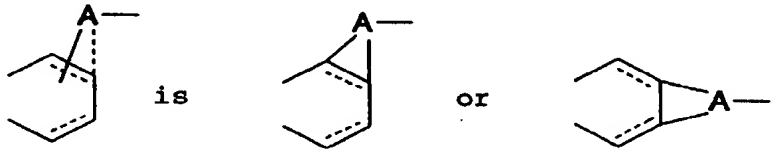
or a non-toxic acid thereof.

2. A compound according to claim 1, wherein



in which A has the same meaning as defined in claim 1.

3. A compound according to claim 1, wherein



in which A has the same meaning as defined in claim 1.

4. A compound according to claim 1, 2 or 3 wherein B is $-NR^3SO_2$, in which R^3 is as defined in claim 1.

5. A compound according to claim 1, 2 or 3 wherein B is $-SO_2NR^3$, in which R^3 is as defined in claim 1.

6. A compound according to any one of the preceding claims wherein the group

is attached to the 1-position and the group A is attached to the 5-, 6- or 5- and 6-positions.

7. A compound according to claim 1, which is

5-[(2-phenylvinyl)sulfonylaminomethyl]naphthyloxyacetic acid,
5-[(2-phenylvinyl)sulfonylamino]naphthyloxyacetic acid,
6-[(2-phenylvinyl)sulfonylamino]naphthyloxyacetic acid,
6-[(2-phenylvinyl)sulfonylaminomethyl]naphthyloxyacetic acid,
6-[(2,2-diphenylvinyl)sulfonylaminomethyl]naphthyloxyacetic acid,
6-[(2,2-diphenylvinyl)sulfonylamino]naphthyloxyacetic acid,
5-[(2,2-diphenylvinyl)sulfonylaminomethyl]naphthyloxyacetic acid,

5-[2-[(2-phenylvinyl)sulfonylamino]ethyl]naphthyloxyacetic acid,
6-[2-[(2-phenylvinyl)sulfonylamino]ethyl]naphthyloxyacetic acid,
5-[(2,2-diphenylvinyl)sulfonylamino]naphthyloxyacetic acid,
5-[2-[(2,2-diphenylvinyl)sulfonylamino]ethyl]naphthyloxyacetic acid,
5-[2-[(2,2-diphenylvinyl)sulfonylamino]ethyl]naphthyloxyacetic acid,
6-[2-[(2,2-diphenylvinyl)sulfonylamino]ethyl]naphthyloxyacetic acid,
6-[(2-phenylvinyl)sulfonylamino]-5,6,7,8-tetrahydronaphthyloxyacetic acid,
6-[(2,2-diphenylvinyl)sulfonylamino]-5,6,7,8-tetrahydronaphthyloxyacetic acid,
5-[(2-phenylvinyl)sulfonylamino]-5,6,7,8-tetrahydronaphthyloxyacetic acid,
5-[(2,2-diphenylvinyl)sulfonylamino]-5,6,7,8-tetrahydronaphthyloxy acetic acid,
6-[(2-phenylvinyl)sulfonylaminomethyl]-5,6,7,8-tetrahydronaphthyloxy acetic acid,
5-[2-[(2-phenylvinyl)sulfonylamino]ethyl]-5,6,7,8-tetrahydronaphthyl oxyacetic acid,
5-[3-[(2-phenylvinyl)sulfonylamino]propyl]naphthyloxyacetic acid,
5-[3-[(2,2-diphenylvinyl)sulfonylamino]propyl]naphthyloxyacetic acid,
5-[(2-phenylethyl)sulfonylamino]naphthyloxyacetic acid,
5-[2-[(2-phenylethyl)sulfonylamino]ethyl]naphthyloxyacetic acid,
5-(pentylsulfonylamino)naphthyloxyacetic acid,
6-[(2-phenylvinyl)sulfonylaminomethyl]naphth-3-yloxyacetic acid,
5-[2-[(2-phenylethyl)sulfonylamino]ethyl]-7,8-dihydronaphthyloxyacetic acid,
5-[2-[(2-phenylvinyl)sulfonylamino]ethyl]-7,8-dihydronaphthyloxyacetic acid,
6-[(2-phenylvinyl)sulfonylaminomethyl]-5,6,7,8-dihydronaphth-3-yl-oxyacetic acid,
5-[2-[(2,2-diphenylethyl)sulfonylamino]ethyl]naphthyloxyacetic acid,
5-[2-[(2-phenylvinyl)sulfonyl-N-ethylamino]ethyl]naphthyloxyacetic acid,
5-[2-[(2-phenylvinyl)sulfonyl-N-carboxymethylamino]ethyl]-naphthyloxyacetic acid,
5-[2-[[2-(4-methoxyphenyl)-2-phenylethyl]sulfonylamino]ethyl] naphthyloxyacetic acid,
5-[2-[(2-phenylpropyl)sulfonylamino]ethyl]naphthyloxyacetic acid,
5-[2-[(2-cyclohexyl-2-phenylethyl)sulfonylamino]ethyl] naphthyloxyacetic acid,
5-[2-[[2-(4-methoxyphenyl)vinyl]sulfonylamino]ethyl] naphthyloxyacetic acid,
5-[2-[[2-(4-chlorophenyl)-2-phenylvinyl]sulfonylamino]ethyl]-naphthyloxyacetic acid,
5-[2-[[2-(4-chlorophenyl)vinyl]sulfonylamino]ethyl]naphthyloxyacetic acid,
5-[2-[(2-phenylvinyl)sulfonylamino]ethyl]-1-N,N-dimethylaminocarbonylmethyloxynaphthalene,
5-[2-[(2-phenylvinyl)sulfonylamino]ethyl]naphthyloxymethylcarboxamide,
5-[2-[(2-phenylvinyl)sulfonylamino]ethyl]-1-(2-hydroxyethyl)-aminocarbonylmethyloxynaphthalene,
5-[2-[(2-phenylvinyl)sulfonylamino]ethyl]-1-(2-hydroxyethyl)-oxynaphthalene.

8. A compound according to claim 1, which is
6-[(2-phenylvinyl)sulfonylamino]-5,6,7,8-tetrahydrophenanthrene-l-yl-oxyacetic acid.

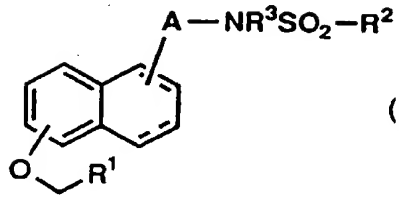
9. A compound according to claim 1, which is

5-[N-(2-phenylethyl)sulfamoyl]naphthyloxyacetic acid,
5-(N-phenylmethylsulfamoyl)naphthyloxyacetic acid,
5-[N-(2,2-diphenylethyl)sulfamoyl]naphthyloxyacetic acid,
5-[N-(4-phenylbutyl)sulfamoyl]naphthyloxyacetic acid,
5-[2-[N-(2,2-diphenylethyl)sulfamoyl]ethyl]naphthyloxyacetic acid,
5-[2-[N-(2-phenylethyl)sulfamoyl]ethyl]naphthyloxyacetic acid.

10. A compound according to claim 1, which is
6-[(2,2-diphenylethyl)sulfamoyl]-5,6,7,8-tetrahydrophenanthren-1-yl-oxyacetic acid.

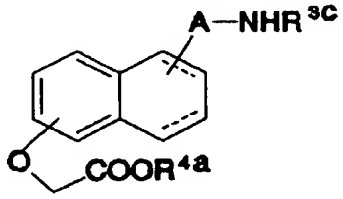
11. A process for the preparation of a compound according to claim 1 which comprises:

(I) when the compound of formula (I) conforms to the formula:



(Ia)

wherein the symbols are as defined in claim 1,
reacting a compound of the formula (II):



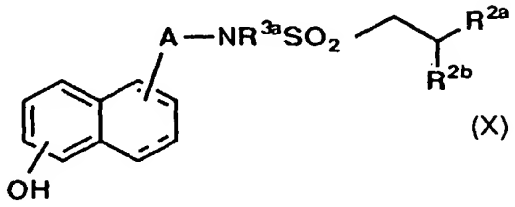
(II)

wherein R^{3c} is hydrogen, C1-4 alkyl or $-CH_2COOR^{4a}$, in which R^{4a} is C1-4 alkyl and the other symbols are as defined in claim 1, with a compound of the formula (III):

$$X^1SO_2\text{-}R^2 \qquad \text{(III)}$$

wherein X^1 is halogen and the other symbols are as defined in claim 1;
(II) by reacting

(A) a compound of the formula (X):



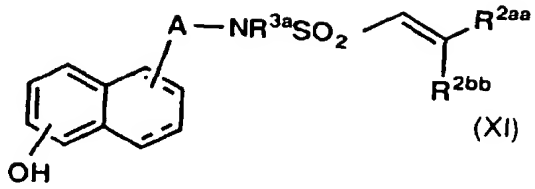
(X)

wherein

is (i) C1-5 alkyl, C2-5 alkenyl or C3-5 alkynyl, or

(ii) C1-5 alkyl, C2-5 alkenyl or C3-5 alkynyl substituted by one, two or three substituents selected from phenyl, C4-7 cycloalkyl or phenyl substituted by one, two or three substituents selected from C1-4 alkyl, C1-4 alkoxy or halogen, and R^{3a} is hydrogen or C1-4 alkyl,
and the other symbols are as defined in claim 1;

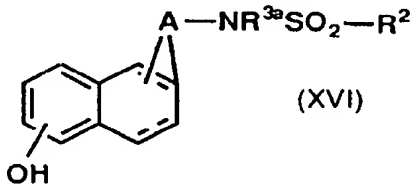
(B) a compound of the formula (XI):



(XI)

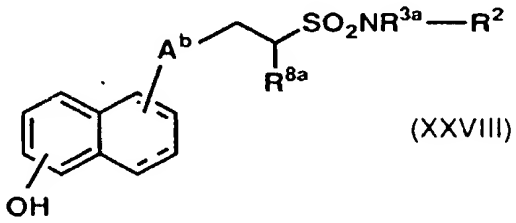
wherein

is (i) C1-5 alkyl, or (ii) C1-5 alkyl substituted by one, two or three substituents selected from phenyl, C4-7 cycloalkyl or phenyl substituted by one, two or three substituents selected from C1-4 alkyl, C1-4 alkoxy or halogen and
the other symbols are as defined in claim 1;
(C) a compound of the formula (XVI):



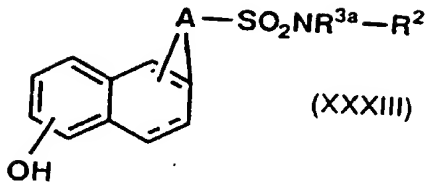
(XVI)

wherein R^{3a} is hydrogen or C1-4 alkyl, and the other symbols are as defined in claim 1;
(D) a compound of the formula (XXVIII):



(XXVIII)

wherein A^b a bond or C1-2 alkylene, R^{8a} is hydrogen or C1-2 alkyl and the other symbols are as hereinbefore defined; or
(E) a compound of the formula (XXXIII):

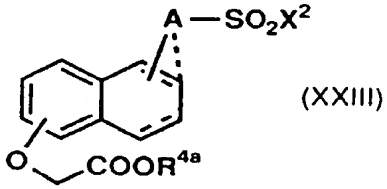

(XXXIII)

wherein all the symbols are as hereinbefore defined;
with a compound of the formula (VI):


(VI)

wherein X^3 is halogen and R^{4a} is as hereinbefore defined, to convert the group OH in the compound of formula (X), (XI), (XVI), (XXVIII) or (XXXIII) into a grouping OCH_2COOR^{4a};

(III) reacting a compound of the formula (XXIII):


(XXIII)

wherein X^2 is halogen and the other symbols are as hereinbefore defined,
with a compound of the formula (XXIV):

$$R^3HN\text{-}R^2 \qquad \text{(XXIV)}$$

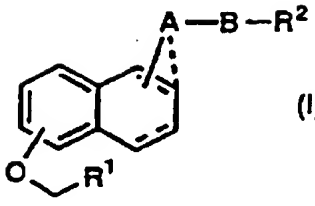
wherein the symbols are as hereinbefore defined;
(IV) optionally converting a group $COOR^{4a}$ in a compound thus obtained into a group COOH, $CONR^5R^6$ or CH_2OH; and
(V) optionally converting a compound of formula (I) thus obtained into a salt thereof.

12. A pharmaceutical composition which comprises, as active ingredient, a naphthyloxyacetic acid derivative of formula (I) as defined in claim 1 or a non-toxic salt thereof, in association with a pharmaceutical carrier or coating.

13. Use of a naphthyloxyacetic acid derivative of formula I as defined in claim 1 but in which R^2 may also represent naphthyl in the manufacture of a medicament for use as a PGE_2 antagonist or against.

Patentansprüche

1. Naphthyloxyessigsäurederivat der Formel (I) :

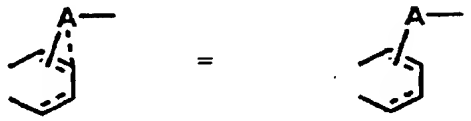

(I)

worin bedeuten:

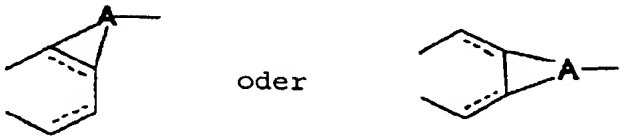
R^1 (i) $-COOR^4$ mit R^4 gleich Wasserstoff oder C_1-C_4-Alkyl;

(ii) $-CONR^5R^6$ mit R^5 und R^6 unabhängig voneinander jeweils gleich Wasserstoff, C_1-C_4-Alkyl oder durch eine Hydroxygruppe substituiertes C_1-C_4-Alkyl, oder

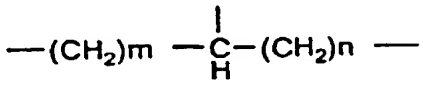
(iii) $-CH_2OH$;



mit A gleich einer Bindung oder C_1-C_4-Alkylen, oder



mit A gleich

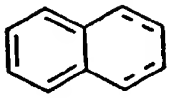


worin m = 0, 1, 2, 3 oder 4, n = 0, 1, 2, 3 oder 4, und m + n = 2, 3 oder 4;

B $-NR^3SO_2-$ oder $-SO_2NR^3-$ mit R^3 gleich Wasserstoff, C_1-C_4-Alkyl oder $-CH_2COOR^7$, worin R^7 für Wasserstoff oder eine Gruppe R^{4a} mit R^{4a} gleich C_1-C_4-Alkyl steht;

R^2 (i) C_1-C_6-Alkyl, C_2-C_6-Alkenyl oder C_2-C_6-Alkinyl, oder

(ii) C_1-C_6-Alkyl, C_2-C_6-Alkenyl oder C_2-C_6-Alkinyl, substituiert mit 1, 2 oder 3 Substituenten, ausgewählt aus Phenyl, C_4-C_7-Cycloalkyl oder ein-, zwei- oder dreifach C_1-C_4-alkyl-, C_1-C_4-alkoxy- oder halogensubstituiertem Phenyl, und in der Formel

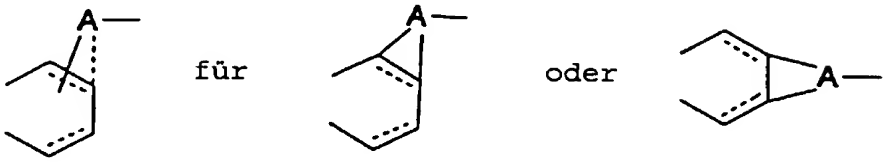


---- eine Einfach- oder Doppelbindung, oder ein nichttoxisches Salz desselben.

2. Verbindung nach Anspruch 1, worin

steht und A die in Anspruch 1 angegebene Bedeutung besitzt.

3. Verbindung nach Anspruch 1, worin

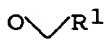


steht und A die in Anspruch 1 angegebene Bedeutung besitzt.

4. Verbindung nach Anspruch 1, 2 oder 3, worin B für $-NR^3SO_2$ mit R^3 in der in Anspruch 1 angegebenen Bedeutung steht.

5. Verbindung nach Anspruch 1, 2 oder 3, worin B für $-SO_2NR^3$ mit R^3 in der in Anspruch 1 angegebenen Bedeutung steht.

6. Verbindung nach einem der vorhergehenden Ansprüche, wobei die Gruppe



an die Position 1 und die Gruppe A an die Positionen 5, 6 oder 5 und 6 gebunden sind.

7. Verbindung nach Anspruch 1, nämlich

5-[(2-Phenylvinyl)sulfonylaminomethyl]naphthyloxyessigsäure,
5-[(2-Phenylvinyl)sulfonylamino]naphthyloxyessigsäure,
6-[(2-Phenylvinyl)sulfonylamino]naphthyloxyessigsäure,
6-[(2-Phenylvinyl)sulfonylaminomethyl]naphthyloxyessigsäure,
6-[(2,2-Diphenylvinyl)sulfonylaminomethyl]naphthyloxyessigsäure,
6-[(2,2-Diphenylvinyl)sulfonylamino]naphthyloxyessigsäure,
5-[(2,2-Diphenylvinyl)sulfonylaminomethyl]naphthyloxyessigsäure,
5-[2-[(2-Phenylvinyl)sulfonylamino]ethyl]naphthyloxyessigsäure,
6-[2-[(2-Phenylvinyl)sulfonylamino]ethyl]naphthyloxyessigsäure,
5-[(2,2-Diphenylvinyl)sulfonylamino]naphthyloxyessigsäure,
5-[2-[(2,2-Diphenylvinyl)sulfonylamino]ethyl]naphthyloxyessigsäure,

5-[2-[(2,2-Diphenylvinyl)sulfonylamino]ethyl]naphthyloxyessigsäure,
6-[2-[(2,2-Diphenylvinyl)sulfonylamino]ethyl]naphthyloxyessigsäure,
6-[(2-Phenylvinyl)sulfonylamino]-5,6,7,8-tetrahydronaphthyloxyessigsäure,
6-[(2,2-Diphenylvinyl)sulfonylamino]-5,6,7,8-tetrahydronaphthyloxyessigsäure,
5-[(2-Phenylvinyl)sulfonylamino]-5,6,7,8-tetrahydronaphthyloxyessigsäure,
5-[(2,2-Diphenylvinyl)sulfonylamino]-5,6,7,8-tetrahydronaphthyloxyessigsäure,
6-[(2-Phenylvinyl)sulfonylaminomethyl]-5,6,7,8-tetrahydronaphthyloxyessigsäure,
5-[2-[(2-Phenylvinyl)sulfonylamino]ethyl]-5,6,7,8-tetrahydronaphthyloxyessigsäure,
5-[3-[(2-Phenylvinyl)sulfonylamino]propyl]naphthyloxyessigsäure,
5-[3-[(2,2-Diphenylvinyl)sulfonylamino]propyl]naphthyloxyessigsäure,
5-[(2-Phenylethyl)sulfonylamino]naphthyloxyessigsäure,
5-[2-[(2-Phenylethyl)sulfonylamino]ethyl]naphthyloxyessigsäure,
5-(Pentylsulfonylamino)naphthyloxyessigsäure,
6-[(2-Phenylvinyl)sulfonylaminomethyl]naphth-3-yloxyessigsäure,
5- [2-[(2-Phenylethyl)sulfonylamino]ethyl]-7,8-dihydronaphthyloxyessigsäure,
5-[2-[(2-Phenylvinyl)sulfonylamino]ethyl]-7,8-dihydronaphthyloxyessigsäure,
6-[(2-Phenylvinyl)sulfonylaminomethyl]-5,6,7,8-dihydronaphth-3-yl-oxyessigsäure,
5-[2-[(2,2-Diphenylethyl)sulfonylamino] ethyl] naphthyloxyessigsäure,
5-[2-[(2-Phenylvinyl)sulfonyl-N-ethylamino]ethyl]naphthyloxyessigsäure,
5-[2-[(2-Phenylvinyl)sulfonyl-N-carboxymethylamino]-ethyl]naphthyloxyessigsäure,
5-[2-[[2-(4-Methoxyphenyl)-2-phenylethyl]sulfonylamino]ethyl]naphthyloxyessigsäure,
5-[2-[(2-Phenylpropyl)sulfonylamino]ethyl]naphthyloxyessigsäure,
5-[2-[(2-Cyclohexyl-2-phenylethyl)sulfonylamino]ethyl]naphthyloxyessigsäure,
5-[2-[[2-(4-Methoxyphenyl)vinyl]sulfonylamino]ethyl]-naphthyloxyessigsäure,
5- [2- [[2- (4-Chlorphenyl)-2-phenylvinyl]sulfonylamino]-ethyl]naphthyloxyessigsäure,
5-[2-[[2-(4-Chlorphenyl)vinyl]sulfonylamino]ethyl]-naphthyloxyessigsäure,
5- [2- [(2-Phenylvinyl)sulfonylamino] ethyl]-1-N,N-dimethylaminocarbonylmethyloxynaphthalin,
5- [2- [(2-Phenylvinyl)sulfonylamino] ethyl]naphthyloxymethylcarboxamid,
5- [2- [(2-Phenylvinyl)sulfonylamino] ethyl]-1-(2-hydroxyethyl)aminocarbonylmethyloxynaphthalin,
5- [2- [(2-Phenylvinyl)sulfonylamino] ethyl]-1-(2-hydroxyethyl)oxynaphthalin.

8. Verbindung nach Anspruch 1, nämlich
6-[(2-Phenylvinyl)sulfonylamino]-5,6,7,8-tetrahydrophenanthren-1-yl-oxyessigsäure.

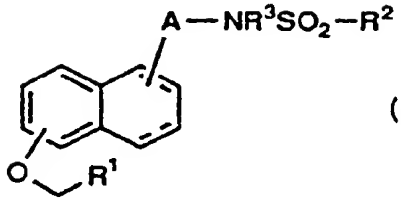
9. Verbindung nach Anspruch 1, nämlich

5-[N-(2-Phenylethyl)sulfamoyl]naphthyloxyessigsäure,
5-(N-Phenylmethylsulfamoyl)naphthyloxyessigsäure,
5-[N-(2,2-Diphenylethyl)sulfamoyl]naphthyloxyessigsäure,
5-[N-(4-Phenylbutyl)sulfamoyl]naphthyloxyessigsäure,
5-[2-[N-(2,2-Diphenylethyl)sulfamoyl]ethyl]naphthyloxyessigsäure,
5-[2-[N-(2-Phenylethyl)sulfamoyl]ethyl]naphthyloxyessigsäure.

10. Verbindung nach Anspruch 1, nämlich
6-[(2,2-Diphenylethyl)sulfamoyl]-5,6,7,8-tetrahydrophenanthren-1-yl-oxyessigsäure.

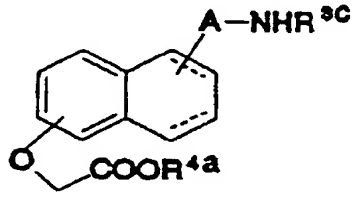
11. Verfahren zur Herstellung einer Verbindung nach Anspruch 1 durch:

(I) - Wenn die Verbindung der Formel (I) der Formel:



(Ia)

entspricht, worin die (verschiedenen Symbole) die in Anspruch 1 angegebene Bedeutung besitzen - Umsetzen einer Verbindung der Formel (II) :



(II)

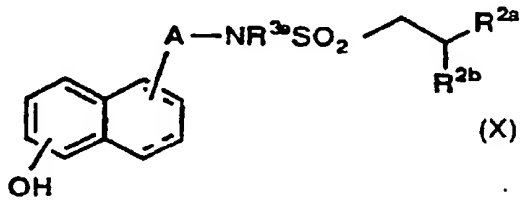
worin R^{3c} für Wasserstoff, C_1-C_4-Alkyl oder $-CH_2COOR^{4a}$ mit R^{4a} gleich C_1-C_4-Alkyl steht und die sonstigen Symbole die in Anspruch 1 angegebene Bedeutung besitzen,
mit einer Verbindung der Formel (III) :

$$X_1SO_2\text{-}R^2 \qquad \text{(III)}$$

worin X^1 für Halogen steht und die sonstigen Symbole die in Anspruch 1 angegebene Bedeutung besitzen;

(II) Umsetzen

(A) einer Verbindung der Formel (X):

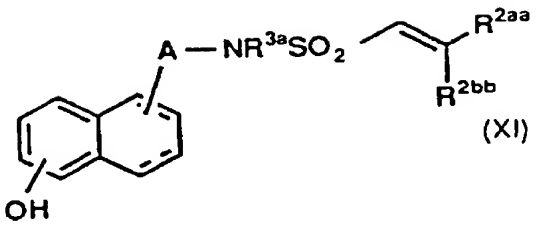


(X)

worin

für (i) C_1-C_5-Alkyl, C_2-C_5-Alkenyl oder C_3-C_5-Alkinyl, oder
(ii) C_1-C_5-Alkyl, C_2-C_5-Alkenyl oder C_3-C_5-Alkinyl, substituiert durch einen, zwei oder drei Substituenten, ausgewählt aus Phenyl, C_4-C_7-Cycloalkyl oder ein-, zwei- oder dreifach C_1-C_4-alkyl-, C_1-C_4-alkoxy- oder halogensubstituiertem Phenyl, steht,
R^{3a} Wasserstoff oder C_1-C_4-Alkyl darstellt und die sonstigen Symbole die in Anspruch 1 angegebene

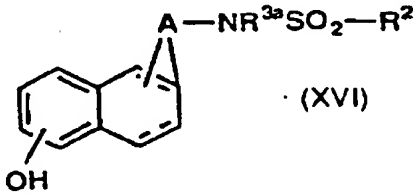
Bedeutung besitzen;
(B) einer Verbindung der Formel (XI) :



(XI)

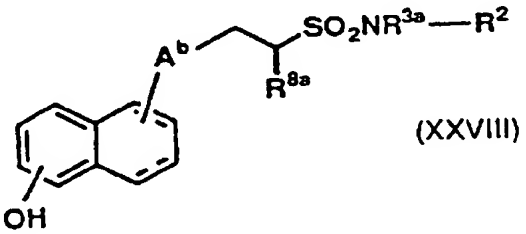
worin

für (i) C_1-C_5-Alkyl, oder
(ii) C_1-C_5-Alkyl, substituiert durch einen, zwei oder drei Substituenten, ausgewählt aus Phenyl, C_4-C_7-Cycloalkyl oder ein-, zwei- oder dreifach C_1-C_4-alkyl-C_1-C_4-alkoxy- oder halogensubstituiertem Phenyl, steht und die sonstigen Symbole die in Anspruch 1 angegebene Bedeutung besitzen;
(C) einer Verbindung der Formel (XVI):



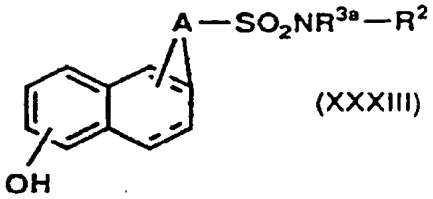
(XVI)

worin R^{3a} für Wasserstoff oder C_1-C_4-Alkyl steht und die sonstigen Symbole die in Anspruch 1 angegebene Bedeutung besitzen;
(D) einer Verbindung der Formel (XXVIII):



(XXVIII)

worin A^b für eine Bindung oder C_1-C_2-Alkylen steht, R^{8a} Wasserstoff oder C_1-C_2-Alkyl darstellt und die sonstigen Symbole die zuvor angegebene Bedeutung besitzen, oder
(E) einer Verbindung der Formel (XXXIII):



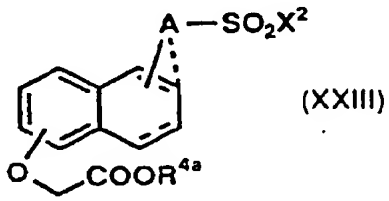
(XXXIII)

worin sämtliche Symbole die zuvor angegebene Bedeutung besitzen,
mit einer Verbindung der Formel (VI):

(VI)

worin X^3 für Halogen steht und R^{4a} die zuvor angegebene Bedeutung besitzt,
zur Umwandlung der Gruppe OH in den Verbindungen der Formeln (X), (XI), (XVI), (XXVIII) oder (XXXIII) in eine Gruppe OCH_2COOR^{4a};

(III) Umsetzen einer Verbindung der Formel (XXIII):



(XXIII)

worin X^2 für Halogen steht und die sonstigen Symbole die zuvor angegebene Bedeutung besitzen,
mit einer Verbindung der Formel (XXIV):

$$R^3HN\text{-}R^2 \qquad \text{(XXIV)}$$

worin die Symbole die zuvor angegebene Bedeutung besitzen;

(IV) gegebenenfalls Umwandeln einer Gruppe $COOR^{4a}$ in einer hierbei erhaltenen Verbindung in eine Gruppe COOH, $CONR^5R^6$ oder CH_2OH, und

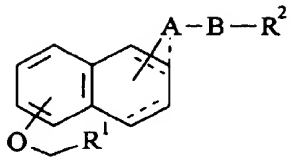
(V) gegebenenfalls Umwandeln einer hierbei erhaltenen Verbindung der Formel (I) in ein Salz derselben.

12. Arzneimittelzubereitung, welche als aktiven Bestandteil ein Naphthyloxyessigsäurederivat der in Anspruch 1 definierten Formel (I) oder ein nichttoxisches Salz desselben in Verbindung mit einem pharmazeutischen Träger oder Überzug enthält.

13. Verwendung eines Naphthyloxyessigsäurederivats der in Anspruch 1 definierten Formel (I), in welcher R^2 auch für Naphthyl stehen kann, bei der Herstellung eines Medikaments zur Verwendung als PGE_2-Antagonist oder -Agonist.

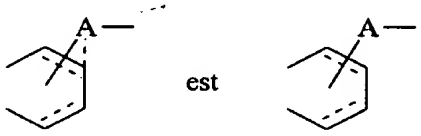
Revendications

1. Un dérivé d'acide naphtyloxyacétique de formule (I) :

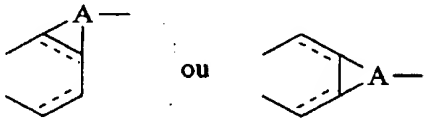


(I)

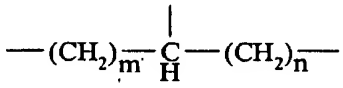
dans laquelle R^1 est (i) $-COOR^4$ dans lequel R^4 est hydrogène ou alkyle en C_{1-4}, (ii) $-CONR^5R^6$ dans lequel R^5 et R^6 sont, chacun indépendamment, hydrogène, alkyle en C_{1-4} ou alkyle en C_{1-4} substitué par un groupe hydroxy ou (iii) $-CH_2OH$;



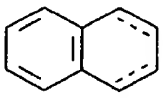
dans lequel A est une liaison ou alkylène en C_{1-4} ou



dans lequel A est



dans lequel m est 0, 1, 2, 3 ou 4, n est 0, 1, 2, 3 ou 4 et m + n est 2, 3 ou 4; B est $-NR^3SO_2-$ ou $-SO_2NR^3-$, dans lequel R^3 est hydrogène, alkyle en C_{1-4} ou $-CH_2COOR^7$ dans lequel R^7 est hydrogène ou un groupe R^{4a}, dans lequel R^{4a} est alkyle en C_{1-4};
R^2 est (i) alkyle en C_{1-6}, alcényle en C_{2-6} ou alcynyle en C_{2-6} ou (ii) alkyle en C_{1-6}, alcényle en C_{2-6} ou alcynyle en C_{2-6} substitué par un, deux ou trois substituants choisis parmi phényle, cycloalkyle en C_{4-7} ou phényle substitué par un, deux ou trois substituants choisis parmi alkyle en C_{1-4}, alcoxy en C_{1-4} ou halogène et dans la formule



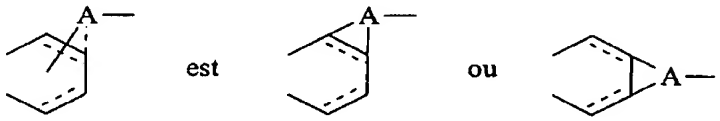
---- est une liaison simple ou une liaison double;

ou un de ses sels d'acide non toxiques.

2. Un composé selon la revendication 1, dans lequel

dans lequel A a la même signification que celle définie dans la revendication 1.

3. Un composé selon la revendication 1, dans lequel



dans lequel A a la même signification que celle définie dans la revendication 1.

4. Un composé selon la revendication 1, 2 ou 3, dans lequel B est $-NR^3SO_2$, dans lequel R^3 est tel que défini dans la revendication 1.

5. Un composé selon la revendication 1, 2 ou 3, dans lequel B est $-SO_2NR^3$, dans lequel R^3 est tel que défini dans la revendication 1.

6. Un composé selon l'une quelconque des revendications précédentes, dans lequel le groupe

est lié en position 1 et le groupe A est lié en positions 5, 6 ou 5 et 6.

7. Un composé selon la revendication 1, qui est

l'acide 5-[(2-phénylvinyl)sulfonylaminométhyl]naphtyloxyacétique,
l'acide 5-[(2-phénylvinyl)sulfonylamino]naphtyloxyacétique,
l'acide 6-[(2-phénylvinyl)sulfonylamino]naphtyloxyacétique,
l'acide 6-[(2-phénylvinyl)sulfonylaminométhyl]naphtyloxyacétique,
l'acide 6-[(2,2-diphénylvinyl)sulfonylaminométhyl]naphtyloxyacétique,
l'acide 6-[(2,2-diphénylvinyl)sulfonylamino]naphtyloxyacétique,
l'acide 5-[(2,2-diphénylvinyl)sulfonylaminométhyl]naphtyloxyacétique,
l'acide 5-[2-[(2-phénylvinyl)sulfonylamino]éthyl]naphtyloxyacétique,
l'acide 6-[2-[(2-phénylvinyl)sulfonylamino]éthyl]naphtyloxyacétique,
l'acide 5-[(2,2-diphénylvinyl)sulfonylamino]naphtyloxyacétique,
l'acide 5-[2-[(2,2-diphénylvinyl)sulfonylamino]éthyl]naphtyloxyacétique,
l'acide 5-[2-[(2,2-diphénylvinyl)sulfonylamino]éthyl]naphtyloxyacétique,
l'acide 6-[2-[(2,2-diphénylvinyl)sulfonylamino]éthyl]naphtyloxyacétique,
l'acide 6-[(2-phénylvinyl)sulfonylamino]-5,6,7,8-tétrahydronaphtyloxyacétique,
l'acide 6-[(2,2-diphénylvinyl)sulfonylamino]-5,6,7,8-tétrahydronaphtyloxyacétique,
l'acide 5-[(2-phénylvinyl)sulfonylamino]-5,6,7,8-tétrahydronaphtyloxyacétique,
l'acide 5-[(2,2-diphénylvinyl)sulfonylamino]-5,6,7,8-tétrahydronaphtyloxyacétique,
l'acide 6-[(2-phénylvinyl)sulfonylaminométhyl]-5,6,7,8-tétrahydronaphtyloxyacétique,
l'acide 5-[2-[(2-phénylvinyl)sulfonylamino]éthyl]-5,6,7,8-tétrahydronaphtyloxyacétique,
l'acide 5-[3-[(2-phénylvinyl)sulfonylamino]propyl]naphtyloxyacétique,

l'acide 5-[3-[(2,2-diphénylvinyl)sulfonylamino]propyl]naphtyloxyacétique,
l'acide 5-[(2-phényléthyl)sulfonylamino]naphtyloxyacétique,
l'acide 5-[2-[(2-phényléthyl)sulfonylamino]éthyl]naphtyloxyacétique,
l'acide 5-(pentylsulfonylamino)naphtyloxyacétique,
l'acide 6-[(2-phénylvinyl)sulfonylaminométhyl]napht-3-yloxyacétique,
l'acide 5-[2-[(2-phényléthyl)sulfonylamino]éthyl]-7,8-dihydronaphtyloxyacétique,
l'acide 5-[2-[(2-phénylvinyl)sulfonylamino]éthyl]-7,8-dihydronaphtyloxyacétique,
l'acide 6-[(2-phénylvinyl)sulfonylaminométhyl]-5,6,7,8-dihydronapht-3-yloxyacétique,
l'acide 5-[2-[(2,2-diphényléthyl)sulfonylamino]éthyl]naphtyloxyacétique,
l'acide 5-[2-[(2-phénylvinyl)sulfonyl-N-éthylamino]éthyl]naphtyloxyacétique,
l'acide 5-[2-[(2-phénylvinyl)sulfonyl-N-carboxyméthylamino]éthyl]naphtyloxyacétique,
l'acide 5-[2-[[2-(4-méthoxyphényl)-2-phényléthyl]sulfonylamino]éthyl]naphtyloxyacétique,
l'acide 5-[2-[(2-phénylpropyl)sulfonylamino]éthyl]naphtyloxyacétique,
l'acide 5-[2-[(2-cyclohexyl-2-phényléthyl)sulfonylamino]éthyl]naphtyloxyacétique,
l'acide 5-[2-[[2-(4-méthoxyphényl)vinyl]sulfonylamino]éthyl]naphtyloxyacétique,
l'acide 5-[2-[[2-(4-chlorophényl)-2-phénylvinyl]sulfonylamino]éthyl]naphtyloxyacétique,
l'acide 5-[2-[[2-(4-chlorophényl)vinyl]sulfonylamino]éthyl]naphtyloxyacétique,
le 5-[2-[(2-phénylvinyl)sulfonylamino]éthyl]-1-N,N-diméthylaminocarbonylméthyloxynaphtalène,
le 5-[2-[(2-phénylvinyl)sulfonylamino]éthyl]naphtyloxyméthylcarboxamide,
le 5-[2-[(2-phénylvinyl)sulfonylamino]éthyl]-1-(2-hydroxyéthyl)aminocarbonylméthyloxynaphtalène,
le 5 -[2-[(2-phénylvinyl)sulfonylamino]éthyl]-1-(2-hydroxyéthyl)oxynaphtalène.

8. Un composé selon la revendication 1, qui est l'acide 6-[(2-phénylvinyl)sulfonylamino]-5,6,7,8-tétrahydrophénanthrén-1-yl-oxyacétique.

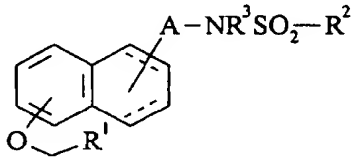
9. Un composé selon la revendication 1, qui est

l'acide 5-[N-(2-phényléthyl)sulfamoyl]naphtyloxyacétique,
l'acide 5-(N-phénylméthylsulfamoyl)naphtyloxyacétique,
l'acide 5-[N-(2,2-diphényléthyl)sulfamoyl]naphtyloxyacétique,
l'acide 5-[N-(4-phénylbutyl)sulfamoyl]naphtyloxyacétique,
l'acide 5-[2-[N-(2,2-diphényléthyl)sulfamoyl]éthyl]naphtyloxyacétique,
l'acide 5-[2-[N-(2-phényléthyl)sulfamoyl]éthyl]naphtyloxyacétique.

10. Un composé selon la revendication 1, qui est l'acide 6-[(2,2-diphényléthyl)sulfamoyl]-5,6,7,8-tétrahydrophénanthrén-1-yl-oxyacétique.

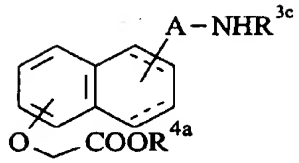
11. Un procédé pour la préparation d'un composé selon la revendication 1, qui comprend:

(I) lorsque le composé de formule (I) est conforme à la formule:



(Ia)

dans laquelle les symboles sont tels que définis dans la revendication 1, la réaction d'un composé de formule (II) :



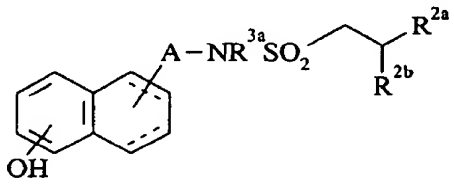
(II)

dans laquelle R^{3c} est hydrogène, alkyle en C_{1-4} ou $-CH_2COOR^{4a}$, dans lequel R^{4a} est alkyle en C_{1-4} et les autres symboles sont tels que définis dans la revendication 1, avec un composé de formule (III) :

$$X^1SO_2\text{-}R^2 \qquad \text{(III)}$$

dans laquelle X^1 est halogène et les autres symboles sont tels que définis dans la revendication 1;
(II) la réaction

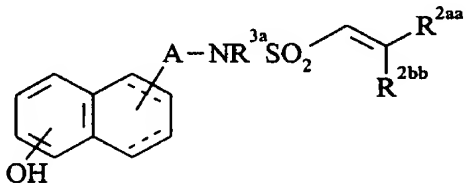
(A) d'un composé de formule (X) :



(X)

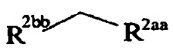
dans laquelle

est(i) alkyle en C_{1-5}, alcényle en C_{2-5} ou alcynyle en C_{3-5}, ou (ii) alkyle en C_{1-5}, alcényle en C_{2-5} ou alcynyle en C_{3-5} substitué par un, deux ou trois substituants choisis parmi phényle, cycloalkyle en C_{4-7} ou phényle substitué par un, deux ou trois substituants choisis parmi alkyle en C_{1-4}, alcoxy en C_{1-4} ou halogène, et R^{3a} est hydrogène ou alkyle en C_{1-4},
et les autres symboles sont tels que définis dans la revendication 1;
(B) d'un composé de formule (XI) :



(XI)

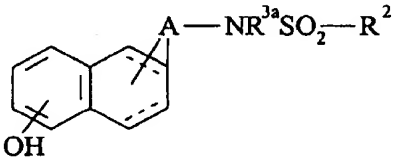
dans laquelle



est (i) alkyle en C_{1-5} ou

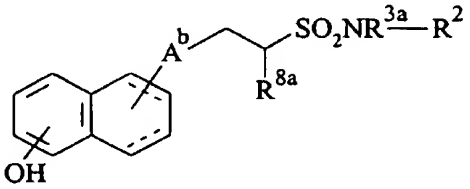
(ii) alkyle en C_{1-5} substitué par un, deux ou trois substituants choisis parmi phényle, cycloalkyle en C_{4-7} ou phényle substitué par un, deux ou trois substituants choisis parmi alkyle en C_{1-4}, alcoxy en C_{1-4} ou halogène et les autres symboles sont tels que définis dans la revendication 1;

(C) d'un composé de formule (XVI) :



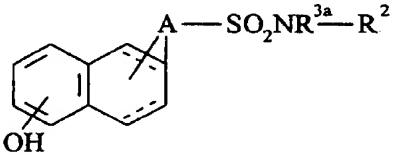
(XVI)

dans laquelle R^{3a} est hydrogène ou alkyle en C_{1-4} et les autres symboles sont tels que définis dans la revendication 1;
(D) d'un composé de formule (XXVIII) :



(XXVIII)

dans laquelle A^b est une liaison ou un alkylène en C_{1-2}, R^{8a} est hydrogène ou alkyle en C_{1-2} et les autres symboles sont tels que définis précédemment; ou
(E) d'un composé de formule (XXXIII) :



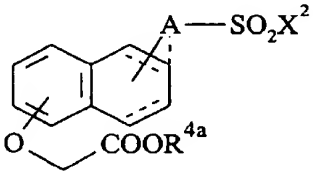
(XXXIII)

dans laquelle tous les symboles sont tels que définis précédemment; avec un composé de formule (VI) :

(VI)

dans laquelle X^3 est halogène et R^{4a} est tel que défini précédemment, afin de convertir le groupe OH dans le composé de formule (X), (XI), (XVI), (XXVIII) ou (XXXIII) en un groupement OCH_2COOR^{4a};

(III) la réaction d'un composé de formule (XXIII) :



(XXIII)

dans laquelle X^2 est halogène et les autres symboles sont tels que définis précédemment, avec un composé de formule (XXIV) :

$$R^3HN\text{-}R^2 \qquad \text{(XXIV)}$$

dans laquelle tous les symboles sont tels que définis précédemment;
(IV) la conversion éventuelle d'un groupe $COOR^{4a}$ dans un composé ainsi obtenu en un groupe COOH, $CONR^5R^6$ ou CH_2OH; et
(V) la conversion éventuelle d'un composé de formule (I) ainsi obtenu en un de ses sels.

12. Une composition pharmaceutique qui comprend, en tant qu'ingrédient actif, un dérivé d'acide naphtyloxyacétique de formule (I) telle que définie dans la revendication 1 ou un de ses sels non toxiques, en combinaison avec un support ou un enrobage pharmaceutique.

13. Utilisation d'un dérivé d'acide naphtyloxyacétique de formule (I), telle que définie dans la revendication 1 mais dans laquelle R^2 peut également représenter naphtyle, dans la préparation d'un médicament pour une utilisation en tant qu'antagoniste ou agoniste de PGE_2.